GRANULOMATOUS DISEASES OF THE INTESTINE *

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MY task is to consider a group of granulomatous disorders of the alimentary tract which have in common an unknown ætiology. The alimentary tract may also be affected by such specific granulomatous conditions as actinomycosis, amœbiasis, tuberculous disease, and lymphogranuloma; and these I shall not consider. What concerns me is Crohn's disease, ulcerative colitis, and the rarer enterocolitis.

Nomenclature

First let me take a problem—how can Crohn's disease be distinguished from ulcerative colitis? Moreover, is there any point in such a distinction? To answer the second question first: these two conditions may have entirely different origins despite contemporary opinion to the contrary, for one of the striking features of Crohn's disease is the severe hypertrophic type of reaction which is manifest in the thickened wall, seen microscopically to be due to œdema and what has been termed (but not determined as far as I know) as collagen. The very appearance makes hypersensitivity spring to mind. Per contra the intestinal wall in ulcerative colitis, though slightly thickened when the disease is not acutely active, becomes thinner and thinner as ulceration, starting in the mucosa, proceeds outwards; there is no macroscopic suggestion of a hypersensitivity reaction, though between muscularis mucosæ and smooth muscle what passes for collagen may sometimes be seen microscopically; the amount of this is less than in Crohn's disease. The difference is obvious to the naked eye, but less obvious when the minutiæ of the tissue are seen. It would be wise to keep these differences in mind until the ætiology is known, since discovery of the cause of each might be retarded by a unitarian theory—as happened with venereal disease. A more practical reason is that treatment is different, not only because of the differing predilection of anatomical site, but also because of the difference in response to treatment.

Can, therefore, Crohn's disease be distinguished from ulcerative colitis? It is perhaps unfortunate that Crohn's disease was originally described in the small intestine and the title terminal ileitis applied to it; this was later changed to regional enteritis when the disease was detected higher in the intestine. In the land of its discovery, doubtless owing to the modesty of Dr. Burrill B. Crohn himself, it has never been termed " Crohn's disease "; this is a pity for the title regional ileitis has tended to separate the disease from the large intestine at least in the minds of those who work on the other side of the Atlantic. Thus any non-specific lesion in the large intestine is colitis, and, ipso facto, ulcerative colitis or a variant of that disorder. Thus Bargen can speak of regional colitis and leave more than an impression that a condition which approximates to Crohn's disease is a form of ulcerative colitis (fig. 1) (Bargen and Weber 1930, Neuman, Bargen, and Judd 1954). Thus, too, right-sided colitis has been regarded as ulcerative colitis though the epicentre of ulcerative colitis usually lies in the descending colon; and the small-intestinal features of right-sided colitis have long passed unnoticed. It seems as though the ileocæcal valve has all the importance of a full-stop in our ætiological conception of the disease: a full-stop which ought not to be there except perhaps in ulcerative colitis—and then it begins the sentence. This limited conception is further compounded by the fact that at the Mount Sinai Hospital, where Crohn first detected the condition, it is considered only rarely to attack the colon initially: in no more than 5% of cases according to Crohn, unless by contiguity with the primary small-bowel lesion and fistula formation between the two or at a recurrence following surgery—resection in particular.

Fig. 1—Barium enema showing localised colitis of Crohn's type in sigmoid region.

Fig. 2—Case of Crohn's disease: *a*, ulceration of the cæcum; *b*, appearances at barium enema.

This was one of the provocative thoughts with which Dr. Crohn left us on his visit to this country two years ago, and it stimulated me to examine the cases on the register of our gastroenterological service in Birmingham. After excluding all cases in which the evidence of the site of the primary

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lesion was insufficient (many had come to us with recurrences following surgery elsewhere) 121 cases could be divided into: (1) 62 with the initial lesion confined to small intestine or above, 14 with high lesions (2 duodenal and 1 gastric) and 48 ileal; and (2) 59 with initial colonic involvement not due to fistulous extension and not following previous resection, comprising 40 ileocæcal, 12 ileal and colonic in skip lesions, and 7 in the colon alone.

How could the 7 involving colon alone be distinguished from ulcerative colitis? Chiefly by the naked-eye appearances: in Crohn's disease the intestine is thicker than it is usually in ulcerative colitis, in which thickening is apparent only after the bowel has been defunctioned by ileostomy; in Crohn's disease the ulcers often have a more elongated and serpiginous appearance with hypertrophy at their edges almost to pseudopolypoid dimensions (fig. 2). The mucosa between ulcers appears relatively normal in Crohn's colitis, but not in ulcerative colitis apart from those segments of bowel which sometimes remain unaffected. The lymph-glands in ulcerative colitis are distinctive; for along the marginal vessel and vasa recta they are abnormal, being shotty but not more than about a centimetre in diameter, while Crohn's disease is accompanied by grosser lymphadenoid hypertrophy not usually so prominent peripherally as proximally in the mesentery. This descriptive differentiation is, I appreciate, unsatisfying and will not convince the sceptic, but in the absence of distinctive biochemical test or any histological sign—and there is nothing specific about the cellular appearances to distinguish one disease from the other—there is, as yet, no better way.

It was heartening therefore to discover an identity of experience at St. Mark's Hospital (Morson 1958). By way of confirmation I can only add that in 2 of the 7 patients with Crohn's disease affecting the colon alone I operated expecting to find ulcerative colitis and totally excised the large intestine, since owing to rectal involvement anastomosis was out of the question. Both later developed typical ileal lesions. In 2 other patients total colitis has followed primary lesions in the ileum. In all 4 the appearances were as I have described.

These matters are controversial, and necessarily so since they represent a change in approach. A third entity, which Dr. Trevor Cooke and I have seen and described as enterocolitis (Brooke 1953, Cooke and Brooke 1955), has proved even more controversial—so much so that I believe London has not yet accepted it though I know that cases have been seen there. This rare condition has hitherto been associated with ulcerative colitis, from which it differs in that it affects the right side—and is accompanied by small-bowel dysfunction reflected in steatorrhœa—in contrast to ulcerative colitis even with secondary ileitis. Templeton has referred to a similar condition (Crohn et al. 1959). 34 cases have been recorded in Birmingham and all have had steatorrhœa. Dr. Cooke and I feel that this entity resembles Crohn's disease more closely than ulcerative colitis, but the striking thickening is absent; Templeton refers to it as non-stenotic enteritis. Moreover, the liver is frequently cirrhotic, and this may be an important point of differentiation since Cooke has yet to see a case of Crohn's disease with cirrhosis, as opposed to fatty infiltration (Cooke 1959).

My mind is open; all three entities may prove to be variants of a disorder or a type of disorder, though I suspect that ulcerative colitis will retain its identity since in its common form, with the subgroup proctitis, it is so essentially a primary condition of the large bowel which does not recur following elimination of that organ. But until we do know, these distinctions should be made to facilitate clinical research; and a clear nomenclature is required. The meaning of "ulcerative colitis" is clear, and "colo-ileitis" should indicate this condition with secondary "reflux" ileitis. The meaning of "Crohn's disease" is clear; and with it the viscus or viscera involved could be named as a definitive suffix, thus—Crohn's ileitis, ileocolitis, and jejunitis, and so on. "Enterocolitis" could be retained for the third entity by those disposed to recognise it.

Liver Damage

Hepatic cirrhosis is usually ascribed to defects of nutrition; yet where ulceration bites deep into intestinal wall laying open vessels dilated by inflammation there seems to be a possible explanation so obvious that I hardly dare to suggest it. Surely substances unusual to the liver and portal system could escape from the intestinal lumen causing changes either by direct toxicity or through sensitisation and "auto-"immunological effects?

I have been trying to assess the extent to which bacterial leak may take place and its relation to liver damage. Though past reports have indicated that portal bacteræmia may not be unusual, in a small pilot study (Brooke and Slaney 1958) the control series of samples of portal blood taken at laparotomy for disorders other than those affecting the colon were sterile, as were also those from cases of colonic disorder other than ulcerative colitis (though I think that with more cases in this group we would have had positive results). 4 out of 9 of the ulcerative-colitis group showed portal bacteræmia. I use the term "bacteræmia" advisedly since I have yet to see portal pyæmia and liver abscesses in ulcerative colitis. In 2 cases we have even grown the same organism from a liver-biopsy specimen as was obtained from the portal blood, and yet those patients had no suggestion of cellular changes associated with infection in the liver. The reticulo-endothelial system of the liver appears to be capable of dealing with the organisms. Nevertheless the organ does not go unscathed, for it is in these cases with gross penetration of the wall—and therefore those especially prone to portal bacteræmia—that jaundice tends to occur. Of 220 cases operated upon by me 17 have developed jaundice, 3 preoperatively, 2 late postoperatively, and 12 in the immediate postoperative period—usually in the first twenty-four hours. It was this incidence of postoperative jaundice (which has been proved in each case not to be due to hæmagglutination) that first made me consider portal bacteræmia, since it seemed possible that manipulation might facilitate the passage of organisms, and more, to the liver. Since undertaking portal culture as a routine, of 44 cases culture has been positive in 14, in 7 of which jaundice developed. In 2 patients with preoperative jaundice organisms similar to those found in the portal blood were grown from the liver. Yet it may not be the organisms which are attacking the liver, for surely metastatic abscesses would sometimes be observed if this were so? The bacteria may only be the indicators of the leak into portal veins; chemical factors could account for the appearances of perilobular fatty necrosis and later post-necrotic cirrhosis. The granulomatous disorders, therefore, may shed light upon the ætiology of cirrhosis generally—particularly if, as Cooke avers, cirrhosis is not found in Crohn's disease, but only fatty degeneration (portal culture though negative has been done in too few cases of Crohn's disease for the negative results in my control series to be of any significance). Why cirrhosis in the one and not the other?

Obstruction

The root cause of obstruction in Crohn's disease and in ulcerative colitis is identical; yet the clinical presentation and management are very different. In neither disease is obstruction due to a stricture, though it is partly due to stenosis in Crohn's disease, and very rarely carcinoma may lead to obstruction in ulcerative colitis—rarely because the large-bowel contents are fluid. In both, obstruction is the outcome of loss of intestinal motility through a length of intestine so long as to defeat the power of the intestine proximal to it to project its contents through the defective area. In Crohn's disease there is a further factor: chronic potassium loss from prolonged diarrhœa leads to a considerable reduction in total exchangeable potassium (Cooke 1955) with consequent weakening of the power of contraction of that part of the intestine which retains motility. This is an important point which has received insufficient emphasis, for it suggests that potassium restoration is all that is required to overcome an acute obstructive episode in Crohn's disease—and this is so. It is now a long time since I have had to operate as an emergency on account of obstruction in this disease; the acute attack can always be overcome by electrolyte restoration to permit operation as an elective procedure at a later day if necessary—and it is not always necessary. A useful sign indicating that further operation is likely to be required is a succussion splash, derived from the dilated ileum even after the symptoms of the obstructive episode have abated.

Not so with ulcerative colitis: obstruction is an urgent indication for emergency surgery of the most arduous nature (primary colectomy, in fact).

In severe ulcerative colitis, as disintegration of the bowel wall proceeds, two things happen: where the colon is normally in close and constant contact with the parietes, adherence takes place to the parietal peritoneum, which then becomes incorporated and performs the function of the bowel wall. This is seen usually in sigmoid, in cæcum less commonly; but in the transverse colon such adherence is rare, and instead there is more commonly dilatation which may become extensive. It has been suggested that such dilatation might be due to potassium loss from diarrhœa; but this can hardly be so, for histological examination of the colon wall shows such destruction of muscle that neither is contraction possible nor can the chemical changes associated with contraction be effective. Moreoever, distension due to hypokalæmia, as in sprue, affects the small intestine rather than the large. In truth what occurs is that a flabby friable wall simply gives way under the weight of its fluid contents and the tension of intestinal gas. It is significant that the transverse colon is chiefly affected, for this is a dependent loop and with loss of contractility becomes a reservoir or sump. It has no power to pass its contents on round the hump of the splenic flexure and on to the descending colon. A sort of retention with overflow then ensues, and obstruction builds up behind. In a relatively short time the small intestine is overwhelmed and can no longer eject its contents through the amotile reaches ahead. A situation of intestinal obstruction has developed with all the signs of obstruction of the lower small bowel—vomiting, abdominal cramps, central distension even with a ladder pattern in addition to the distinctive transverse colonic dilatation. It is this which deceived physicians no more than ten years ago into thinking that when abdominal distention was seen a stricture had developed, for the clinical picture closely mimics mechanical obstruction. The number of stools becomes reduced as the condition advances, and I have seen complete cessation of wind and fæces in the fully developed state—but no stricture on laparotomy, only a colon robbed of all power.

In complete contrast to Crohn's disease these signs of obstruction are urgent indications for operation, which cannot be delayed any longer than is necessary to correct dehydration as far as possible and to restore some semblance of chemical balance; for perforation is about to occur, if it has not already done so. This is a difficult point to decide since perforation may be clinically silent in this disease, but a point of no importance: the indication for operation is a distended amotile bowel with mechanical obstruction in which perforation is either impending or has already taken place. The effects of perforation are sometimes bizarre.

I have seen 2 patients in whom tension pneumoperitoneum developed, respiratory movements transmitting through a minute hole the tension variations that produced the one-way-valve effect. In one of these cases the abdomen was so distended that indentation was impossible. When the abdomen was opened fæces began to exude from the hole into an unsoiled peritoneal cavity, which had clearly been protected by the high cœlomic tension, thus accounting for survival at the sixth day after perforation. The patient also survived primary colectomy.

Peritoneal soiling is the greatest concern of the surgeon when he comes to remove the colon in this condition—and remove it he must since ileostomy alone as an emergency measure does not remove the hazard of perforation or hæmorrhage and often cannot be accomplished without damage to the colon necessitating colectomy, since the bowel wall is too friable to permit closure of the hole. To achieve colectomy without soiling has been extremely difficult; not so long ago (Brooke 1956) my experience in the matter was bitter enough to make me look again at the possibility of emergency ileostomy alone. I realised that the secret was to empty the bowel before mobilising it; the passage of a tube per rectum is unsatisfactory, so a hole in its wall is required for the introduction of a sucker but the stitches necessary for closure of this hole invariably cut out. Now I have a solution. At areas where disintegration has caused parietal peritoneum to become part of the bowel wall, it is necessary to remove peritoneum with the intestine; any attempt to find a plane of cleavage between the two leads to penetration of the colon. If the incision which finds the extraperitoneal plane is made through the parietal peritoneum at $^1/_2$–1 in. from its junction with what remains of the colon wall, a leaf is provided which can then be used as a seal. Access for suction can then be made through a hole placed so as to lie under this, and the mattress stitches passed from without to hold this leaf down to the colon over the hole do not cut out (fig. 3). This manœuvre has transformed the results in these desperate cases.

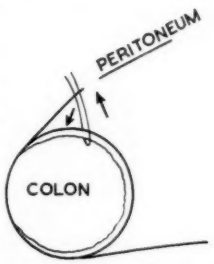

Fig. 3—Diagram to demonstrate method of approach to bowel lumen for preliminary evacuation.

Treatment

A surgeon's vision of the therapeutic advance due to corticosteroid therapy is limited by the fact that he seldom

has the chance to apply it before a physician, and is biased by the fact that he receives in particular those patients with ulcerative colitis who have failed to respond to hormones; but there can be no doubt about the objectivity of the results described in the Medical Research Council trials of cortisone and corticotrophin (Truelove and Witts 1954, 1955, 1959). The physician can, I believe, sometimes recognise cases of ulcerative colitis which will not do well with hormone treatment from radiographic evidence of penetration deep to the muscularis mucosæ, revealed by the collar-stud appearance of intramural abscess cavities and by "pseudo-haustration" (Brooke 1956). In summary, the steroids may induce remission and prolong its duration in ulcerative colitis but may not otherwise alter the natural tendency to recurrence; while in entero-colitis they appear to bring the condition within the bounds of surgery, for Dr. Cooke and I have 3 cases whose small-bowel disorder together with malabsorption was corrected by long-continued steroid therapy, enabling the colonic lesions to be treated by surgery as though the disorder was colitis.

Chemotherapeutic agents have a secondary place which may fortify steroid therapy—it at least is rational to attempt to protect the patient from the effects of removing his inflammatory and immunological barriers. Only salicylazosulphapyridine has, in my experience, a place in its own right as a primary therapeutic measure, and then only in that subgroup of ulcerative colitis—circumscribed proctitis and proctosigmoiditis.

Surgery has little place in enterocolitis unmodified by corticosteroids since eradication would necessitate extirpation of most of the large and small intestine; operation is needed only for intractable incapacitating diarrhœa.

As the natural history of Crohn's disease has unfolded itself in the past quarter-century, optimism has been tempered by results and we no longer regard excision of the gross lesion as a procedure of choice which will lead to cure; for after operation the disease smoulders on to recur in a high proportion of cases. Nevertheless approximately 80% of patients with this condition come to operation (Crohn 1958); and, but for surgery, this disease, which is not particularly lethal in itself, would cause a higher morbidity and mortality due to complications. "Holding operations" are necessary to overcome repeated obstruction, internal and anorectal fistulæ, disabling diarrhœa, and wasting due partly to steatorrhœa and in some cases to severe protein loss from the ulcerated bowel.

There are two schools of thought regarding the method of choice. At Mount Sinai Hospital, Crohn and his colleagues favour anastomosis as an operation of exclusion, since their statistics show a lower operative mortality vis-à-vis resection and no higher recurrence-rate. When Crohn himself posed the question in a panel discussion by the American Gastroenterological Association (Crohn et al. 1959) Dr. Richard Catell and I wholeheartedly favoured resection, except for duodenal involvement where technical considerations demand anastomosis. The advantages of resection lie in the removal of a gross lesion which even if bypassed may (though I admit rarely) fail to settle and so may later give rise to abscess or fistula. In the group who tend to lose much protein this feature may persist. Moreover in some cases the lesion cannot be properly assessed without a dissection which inevitably leads to resection. For example, I recently dealt with a recurrence causing three separate internal fistulæ, one being between jejunum and colon and communicating with an abscess about to cause stomach to be included in the fistula; anastomosis would have been of little avail. Sometimes the intestines are so matted together that dissection of the lesion is required in order to define the appropriate loops; it is safer to remove the affected portion of bowel after it has been dissected than to rely on anastomosis to protect an area which operative interference has rendered more prone to leakage.

Whether exclusion or resection is preferred, it is important to preserve as much small intestine as possible; for these patients have an underlying generalised small-bowel defect disposing them to steatorrhœa which can only be accentuated by removing sections of gut from the functioning circuit. Furthermore, further resections may be necessary later.

The most difficult cases to manage are those with Crohn's colitis. I have been forced to excise the whole large intestine in 4; 2 of these patients subsequently had ileal recurrences above the ileostomy stoma, and in 1 this was successfully treated with cortisone. When ileorectal anastomosis can be performed the chief symptom—diarrhœa—usually persists to a disabling degree despite improvement in weight and general health and despite corticoid therapy.

Unlike Crohn's disease ulcerative colitis can be cured—cured by colectomy, since secondary ileitis resolves even when an ileostomy stoma is placed in the affected area. Some surgeons shrink from this extensive operation; and controversy over it has been revived in the past five to ten years by those who regard ileostomy as a disaster. Disaster it was until the advent of the adherent bag, and more dangerous until the adoption in the past ten years of mucosal eversion, which has done much to eliminate morbidity and mortality due to the ileostomy dysfunction (Warren and McKittrick 1951) which accompanied serositis at the exposed surface of the terminal ileum. Those who advocate ileorectal anastomosis as a routine do so on the ground that an ileostomy is a disability—which it is not if correctly performed and properly looked after. In the second and third decades of this century anastomosis followed by removal of the colon was the method practised, but it had to be abandoned. While admiring the skill and pertinacity of the protagonists of ileorectal anastomosis, I am not impressed by the argument that to achieve success with this method it is necessary to remove the last inch of colon (Aylett 1953); for what possible weakness can there be which is specific to the last inch of the colon and not to the first inch of the rectum? Who can tell where the colon ends and the rectum begins? Is not the upper third of the rectum embryologically colon?

But there are sound positive reasons for regarding total excision as the method of choice, reserving ileorectal anastomosis for the rare case with no rectal involvement, for children until they are old enough to manage an ileostomy, and for those with mental deterioration. All the complications of the disease can persist, recur, or arise de novo with only the rectum retained; in addition I have seen acute ileitis above the anastomosis cause an acute emergency when a recrudescence beset the rectum. Perhaps the most disturbing feature is the carcinoma hazard, which remains wherever there is large bowel either in or out of circuit. It is now well known that this hazard increases with the duration of the disease, less known that the incidence is 30 times that in a similar population with previously normal bowel (Weckesser and Chinn 1953). In Birmingham, with the aid of Mr.

Geoffrey Slaney and Dr. J. A. H. Waterhouse, the published reports of carcinoma complicating the disease have been analysed: such cases amount to almost 500, of which 286 are available for study, making 304 with 18 of our own cases. Thorough statistical analysis has revealed that the five-year survival once the disease has been treated is no more than 18–19%. Carcinoma with its insidious clinical onset may be masked by the parent disease; it gives rise to little if any radiographic change; and it may develop when ulcerative colitis has been quiescent for years (Svartz and Gillnäs 1958), and the symptoms of the carcinoma may be mistaken by patient and clinician as those of recurrent ulcerative colitis alone. Of the 304 cases, 34 died from carcinoma in defunctioned colon, 11 from carcinoma in a retained but nonfunctioning rectum, and 3 from carcinoma in the rectum below an ileorectal anastomosis. All the evidence seems to suggest that, once ulcerative colitis has done serious damage, cancer is a growing hazard with increasing duration of the disease whether the bowel is maintained in circuit or not. Ileorectal anastomosis has often to be undertaken at a stage when cancer is not in mind; but the rectum is then retained and is more likely to become the site of cancer as each year passes.

The surgery of ulcerative colitis has progressed further than similar treatment for the other non-specific granulomas, not only because it is more decisive but because much thought has been given to aftercare. The chemical disturbances which immediately follow ileostomy can now be treated accurately; for, despite an early error on my part (Crawford and Brooke 1957, 1958), we now know how much sodium and potassium will be lost per unit volume excreted: as a rough guide in milliequivalents of sodium one-tenth of the volume of ileostomy excreta and of potassium one-hundredth, unless there is ileitis when the potassium loss rises to one in thirty or one in twenty. We realise that adrenal collapse may follow operative stress in patients who have previously received corticoid therapy; we anticipate serious infection, even septicæmia, but not by blunderbuss antibiotic therapy (Slaney and Brooke 1957, 1958). Thus the operative mortality is falling from 5% and the patient mortality from 10%; patients apparently moribund are recovering life, health, and full activity, to which ileostomy is proving no bar even as the years progress from 5 to 10, 15, and even 20 from its institution. From follow-up studies I undertook in 1955 and repeated in recent months it transpires that 92% return to normal activities and remain fully occupied over periods up to as long as 20 years.

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ATHEROSCLEROSIS AND DEFICIENCY OF ESSENTIAL FATTY ACIDS

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DURING the past few years the possible relation between deficiency of essential fatty acids and the development of atherosclerosis has been the subject of much discussion. The debate was to some extent prompted by a paper read in the symposium on atherosclerosis at the University of Minnesota in September, 1955, when we pointed out that the favourable results from a corn-oil diet in the treatment of hypercholesterolæmia might possibly be due to the abundance of essential fatty acids in corn oil.

Like several other investigators, we have since tried to attack the problem by studies on man. We have given healthy volunteers, as well as patients with hypercholesterolæmia, different kinds of fat containing different amounts of polyunsaturated fatty acids, and we have followed the serum-cholesterol level for various periods. It is now established that a diet containing no fat other than butter or coconut fat will raise the serum-cholesterol level, and that replacement of such fat by a corresponding amount of corn oil or other oil containing abundant polyunsaturated fatty acids will have a depressive effect on the cholesterol (Kinsell et al. 1952, Ahrens et al. 1954, Malmros and Wigand 1955, 1957, Beveridge et al. 1956, Bronte-Stewart et al. 1956, Keys et al. 1957).

Though these investigations suggest that polyunsaturated fatty acids tend to prevent the development of hypercholesterolæmia, they provide no conclusive evidence that atherosclerosis is a direct consequence of fatty-acid deficiency. Such short-term experiments on man teach us nothing about what is going on in the vessel walls.

Relatively early in the debate Sinclair (1956) stressed the need for research into the relation of essential fatty acids and atherosclerosis. But few researchers have since performed animal experiments to elucidate this interesting problem.

It has long been known, from the work of Anitschkow and Chalatow (1913) and other Russian investigators, that a high-cholesterol, high-fat diet will produce atherosclerosis in rabbits. Anitschkow and Chalatow used pure cholesterol dissolved in sunflower-seed oil. When the animals were given the oil without addition of cholesterol, no atheromatous lesions developed. They concluded, therefore, that the cholesterol was the active component, and that the sunflower-seed oil served as a solvent.

We now know that the body can synthesise cholesterol, and therefore interest is focused on dietary fat rather than dietary cholesterol.

Cholesterol-free Diet

Recent research has shown that atherosclerosis can be induced in rabbits when there is no cholesterol in the diet.

Steiner and Dayton (1956) showed that hyperlipæmia and atherosclerosis can be produced in rabbits by a diet consisting of 50–70% peanuts without supplementary cholesterol. Lambert et al. (1958) succeeded in producing atherosclerosis in rabbits by feeding them with a purified cholesterol-free diet containing 20% hydrogenated coconut oil.

Independently, a similar method has been devised in the department of medicine, University of Lund, for pro-

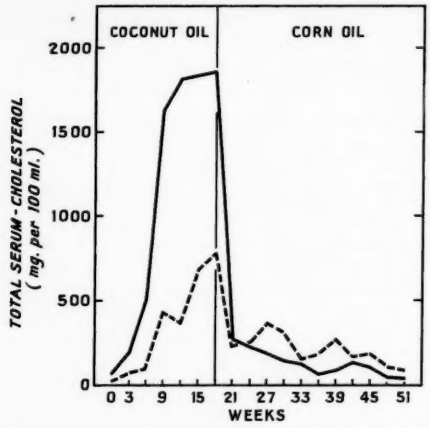


Fig. 1—Total serum-cholesterol in two rabbits fed on a semisynthetic cholesterol-free diet containing hydrogenated coconut fat (8%). After 18 weeks the coconut fat was replaced by corn oil and the cholesterol level fell, first abruptly and then gently towards normal.

ducing atherosclerosis in rabbits. The diet is semi-synthetic and cholesterol-free, and it contains fat in a concentration of 8% (Wigand 1957).

The composition of the diet is:

Sugar ..	.. 12%	Casein ..	.. 25%
Starch ..	.. 17%	Fat ..	.. 8%
Cellulose	.. 19%	Vitamins and salts	

Tablets of 1 g. were prepared. The animals received a daily ration of 25 g. per kg. body-weight, but no supplementary food. They were allowed to drink water ad libitum.

Various kinds of fat were studied. The serum-cholesterol level and the appearance of the vessels were found to vary with the kind of fat in the diet. Milk fat and hydrogenated coconut fat produced distinct hypercholesterolæmia, and within 3–4 months the aorta showed gross changes of the type seen in cholesterol-induced atherosclerosis. Corn oil, cottonseed oil, poppyseed oil, groundnut oil, and rapeseed oil produced only a small rise of serum-cholesterol, and, after an experimental period of 4 months, necropsy revealed no gross lesions in the aorta (Malmros et al. 1958, Malmros and Wigand 1959). When hydrogenated coconut fat was replaced by corn oil the serum-cholesterol fell abruptly (fig. 1).

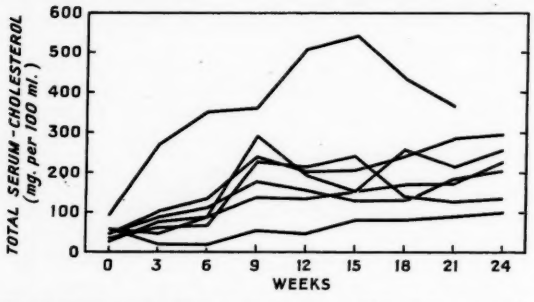


Fig. 2—Total serum-cholesterol in seven rabbits fed on a semi-synthetic cholesterol-free and fat-free diet.

Thus our investigations showed that, under the present experimental conditions, certain fats, such as hydrogenated coconut fat, produced atherosclerosis while liquid vegetable oils did not. In seeking an explanation of this difference one might suggest that coconut fat contains some atherogenic factor, or that it is deficient in essential fatty acids. Possible atherogenic factors are the saturated fatty acids, and particularly those with short carbon chains with lauric acid has 12 carbon atoms, and represents 45% the fat the fatty acids in coconut fat. As to the second possibility be the coconut fat contains only 1% linoleic acid, and even this one is destroyed if the fat is hydrogenated.

In a previous experiment (Malmros and Wigand 1959 mg. p addition of 8% glyceryl trilaurate to the semisynthetic synth basic diet was found to produce a rapid and considerable m-cho rise in the serum-cholesterol. This enhancing effect was that diminished, though not abolished, by addition of corn oil tty a (4%) or linoleic acid (4%).

Cholesterol-free and Fat-free Diet

The possibility of deficiency of essential fatty acids was he qu easy to test with the semisynthetic diet, which the rabbits abbits seemed to like, and which they did not tire of.

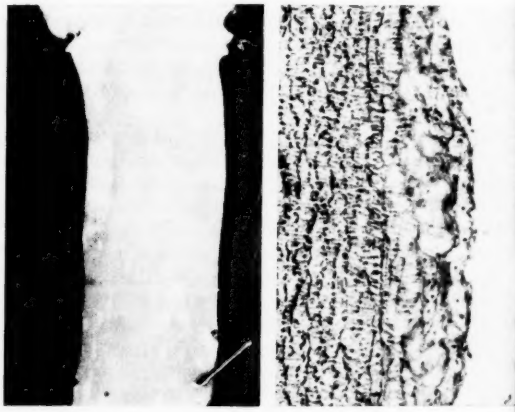


Fig. 3 **Fig. 4**

Fig. 3—Gross aortic lesions in a rabbit fed for 21 weeks on cholesterol-free and fat-free diet. The lesions appear white on the unstained specimen.

Fig. 4—Cross-section of an aortic lesion showing foam-cells intimal fatty accumulations.

Seven rabbits received this cholesterol-free diet with any fat. The serum-cholesterol nevertheless rose re larly—in one animal to as much as 525 mg. per 100 (fig. 2). At necropsy of that rabbit, 21 weeks after beginning of the experiment, the aorta showed the gross changes as in cholesterol-induced atheroscle (fig. 3).

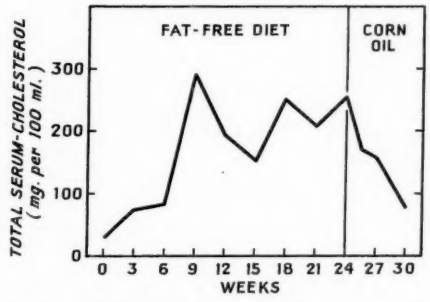


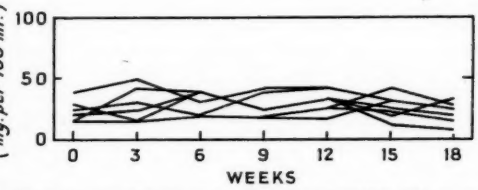
Fig. 5—Total serum-cholesterol in a rabbit fed for 24 weeks on cholesterol-free and fat-free diet. On addition of corn oil (8% the serum-cholesterol dropped rapidly.

icroscopic examination of the intima at the sites of the omatous plaques showed an accumulation of foam-cells with lipoids (fig. 4). The chemical analysis of these lesions the fatty-acid spectrum in the serum and in various organs be the subject of a future paper.

one animal, which had had the fat-free diet for eeks and had developed hypercholesterolæmia (about mg. per 100 ml.), incorporation of corn oil (8%) in the isynthetic diet was followed promptly by a fall in the m-cholesterol (fig. 5). This experiment strongly sug- that the hypercholesterolæmia was due to deficiency tty acids. Similar experiments are in progress with mically pure glyceryl linoleate instead of corn oil.

Discussion

he question remains whether these observations made abbits also hold for man. It has been claimed that iency of essential fatty acids does not occur in adult at any rate. In our experiments the rabbits were onths old—i.e., full-grown—and they seemed to do on the fat-free diet: they had a good appetite and nk water freely, and their body-weight remained prac-



6—Total serum-cholesterol in nine control rabbits fed on an dinary diet (crushed corn, hay, and mangels).

lly constant. They did not show any changes suggest- deficiency of essential fatty acids. In other experiments h the semisynthetic diet containing hydrogenated coco- oil (8%) loss of hair and shabbiness of the fur were etimes noted, but only for a short time. In an experi- t still in progress the animals have had the same diet nore than a year, and as yet no signs of deficiency of tial fatty acids, except hypercholesterolæmia and porary loss of hair, have been observed.

he cholesterol metabolism is obviously greatly in- ced by these experimental conditions under which lesions develop in the aorta within 3 months. When an ordinary diet—i.e., crushed corn, hay, and gels—the serum-cholesterol in rabbits is never above per 100 ml. (fig. 6). This diet is low in fat though o means fat-free, the fat consisting mainly of poly- turated fatty acids. Obviously rabbits normally uire only relatively small amounts of such fatty acids their cholesterol metabolism since they live on a diet poor in fat. But if they are given relatively large ounts of fat of a kind not in their normal diet—i.e., rated fats, such as hydrogenated coconut fat or butter hey cannot quite cope with the extra strain, even if they given large amounts of supplementary polyunsaturated y acids. In an experiment with glyceryl trilaurate %), for example, an addition of 4% pure linoleic acid ed to prevent hypercholesterolæmia.

There might not, after all, be so much difference be- en the mode of reaction of man and of rabbits. If we re to live like Bantu Negroes on a mainly vegetable diet, which the small amounts of fat consisted mainly of yunsaturated fatty acids, our serum-cholesterol would low and atherosclerosis rare. But as long as our diet includes relatively large amounts of milk fat and other animal fat, coconut fat, and hydrogenated fat, the relatively small amounts of polyunsaturated fatty acids consumed simultaneously will not suffice to prevent hypercholesterolæmia. Even such a low cholesterol value as 250–300 mg. per 100 ml. implies a certain degree of hypercholesterolæmia, which will sooner or later result in atherosclerosis.

In young animals full-blown deficiency of essential fatty acids, with skin symptoms, can be produced only by eliminating even the smallest traces of polyunsaturated fats. But one manifestation of deficiency—namely hypercholesterolæmia with subsequent atherosclerosis—can be produced easily even in full-grown rabbits without eliminating all the polyunsaturated fatty acids, provided the diet includes some fat, such as butter, with saturated fatty acids in excess. Thus atherosclerosis can be induced in rabbits by feeding them on a diet with too low a ratio between the polyunsaturated fatty acids and the total amount of fat. This probably also holds for man.

Summary

A semisynthetic diet containing neither cholesterol nor fat induced hypercholesterolæmia and subsequent atherosclerosis in full-grown rabbits. Apart from hypercholesterolæmia, the animals showed no clear signs of deficiency of essential fatty acids. Hypercholesterolæmia disappeared when corn oil (8%) was added to the previously fat-free diet.

The semisynthetic diet with the addition of coconut fat (8%) or butter (8%) also induced hypercholesterolæmia and atherosclerosis.

Glyceryl trilaurate (8%) produced a considerable rise in the serum-cholesterol, which could not be completely abolished by addition of corn oil (4%) or pure linoleic acid (4%). This was probably due to relative deficiency of essential fatty acids.

There is much to suggest that the same nutritional-metabolic changes may develop in man on an unbalanced high-fat diet, and that atherosclerosis is thus a symptom of relative deficiency of essential fatty acids.

These investigations were undertaken as part of a study of atherosclerosis at the medical clinic, University of Lund, supported by the Swedish Medical Research Council. The animal experiments were financed by Margarinbolaget AB, Stockholm, and AB Karlshamns Oljefabriker, Karlshamn.

We are indebted to Dr. G. Wode, director E. Olin, Mr. W. Anderson, chief chemist at Mazetti, A. B. Malmö, Mr. C. Alfons, pharmaceutical chemist at Apoteket Hjorten, Lund, and Mr. P. Möller, engineer at the research laboratory, Karlshamns Oljefabriker, for valuable suggestions and inspiring discussions concerning technical and chemical fat problems. Fig. 4 was kindly provided by Dr. Nils Stormby of the department of pathology, University of Lund.

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CHLORPROPAMIDE IN THE TREATMENT OF DIABETES MELLITUS

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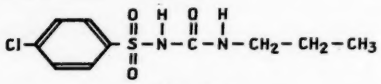
CHLORPROPAMIDE (1-[*p*-chlorobenzenesulphonyl]-3-propyl urea, 'Diabinese') has recently been introduced for the treatment of certain cases of diabetes mellitus. The early work with this compound is reviewed in the *Annals of the New York Academy of Sciences* (1959, **74**, 407). It is absorbed by mouth and excreted unchanged in the urine. The half-life of its pharmacological activity is 35 hours, compared with 3·5 hours for tolbutamide (Stowers et al. 1959). It has no antibacterial activity. The structural formula is as follows:



Methods

Chlorpropamide was administered to 126 diabetics. Approximately 50% of this number had either relapsed or failed to respond to tolbutamide. All patients in whom the apparent beneficial effect of chlorpropamide was thought to be due to better dieting were excluded from the trial. Similarly all cases treated within the first few weeks after diagnosis were first shown to respond poorly to diet. No case was included in which the failure of tolbutamide was considered to be the result of an associated medical condition. A patient was considered to be well controlled on chlorpropamide when the morning specimen of urine was sugar-free and a random blood-sugar at least $1^1/_2$ hours after breakfast was below 210 mg. per 100 ml.

Chlorpropamide was administered as a single daily dose before breakfast to all patients. The initial dose in the great majority of cases was 375 or 250 mg., and this was later reduced according to the patient's progress. A few patients received an initial dose of 500 mg., but this was later found to be unnecessary. The change from insulin to chlorpropamide was effected in two different ways. In a third of the patients the dose of insulin was reduced by 50% and 100–250 mg. of chlorpropamide was administered together with the reduced dose of insulin, which was further reduced over a period of 7–14 days if good results were obtained. In the remainder, the insulin was stopped completely and the first dose of chlorpropamide administered on the following day. All patients were on an unweighed diet at the start of treatment and no change was made in the carbohydrate allowance, which varied from 90 to 200 g. per day.

The patients were seen at 7, 14, and 30 days after the start of treatment. At each visit the blood-sugar was estimated by a modified Nelson technique, and the first specimen of urine passed on waking and the last specimen passed the previous night were tested for glucose content. All patients were weighed at each visit.

Results

The results are shown in table I. It will be seen that the patients were a selected group since 50% had previously failed to respond to tolbutamide or had relapsed after a period of good control on this drug. As with other oral hypoglycæmic agents, chlorpropamide is most effective in the mild, non-ketotic type of diabetic and in those requiring less than 40 units of insulin per day. Good results, however, were obtained with some patients who had previously required as much as 80 units of insulin daily. In these cases the most efficient method of converting to chlorpropamide was by the gradual substitution of insulin as already described. The sudden stoppage of insulin almost invariably led to a relapse in these cases; this is in keeping with the observation that the sulphonyl ureas may have to be administered for as long as 7 days before their full pharmacological effect becomes apparent. Chlorpropamide was ineffective in cases of "insulin insensitivity"—i.e., those middle-aged obese patients who can tolerate large doses of insulin without hypoglycæmic reactions and with little effect on their diabetic control. This group is separate from cases of "insulin resistance" with a demonstrable insulin antibody (Oakley et al. 1959).

Toxic effects developed in only 5 of the 126 cases in this series. 2 of the patients became extremely depressed, and this was relieved by stopping the drug; both patients gave a previous history of a depressive psychosis. A generalised, erythematous macular rash, particularly pronounced in the axillæ and groins, was produced in 2 cases after 10–14 days on treatment, despite good diabetic control. No impairment of hepatic function was found in either case, and the skin manifestations disappeared 3–4 days after the drug was discontinued. Nausea and abdominal discomfort developed in 1 case on chlorpropamide; tolbutamide had previously been shown to have a similar effect in this case. 15 patients on chlorpropamide developed hypoglycæmic symptoms, which in each case were easily controlled by the immediate administration of 10–20 g. of carbohydrate followed by an additional 20 g. at the next meal. This method of treating hypoglycæmic effects was explained to all patients.

17 cases which had relapsed on tolbutamide were treated with chlorpropamide, and of these 15 responded well. In no case did more than 3 weeks elapse between the cessation of tolbutamide and the commencement of chlorpropamide therapy. Of the 2 cases which failed to respond one never received more than 150 mg. a day and the other developed coronary thrombosis a few days after the change of therapy.

Analysis of the patients' ages and the duration of diabetes (table II) in all the cases treated with chlorpropamide shows that these two factors have no bearing

TABLE I—RESULTS OF TREATMENT WITH CHLORPROPAMIDE RELATED TO RESPONSE TO TOLBUTAMIDE

Type of diabetes	Total no. treated	Response to chlorpropamide		Toxic effects	Patients relapsing on tolbutamide			Patients unresponsive to tolbutamide		
		Satisfactory	Failures		No. treated	Response to chlorpropamide		No. treated	Response to chlorpropamide	
						Satisfactory	Failures		Satisfactory	Failures
Mild; no insulin	54	42	12	3	12	10	2	17	9	8
Less than 40 units insulin per day	48	35	13	2	3	3	0	18	12	6
More than 40 units insulin per day	13	6	7	0	1	1	0	10	3	7
Acute ketotic onset	11	6	5	0	1	1	0	3	1	2
Totals	126	89	37	5	17	15	2	48	25	23

TABLE II—RESPONSES TO CHLORPROPAMIDE RELATED TO DURATION OF DIABETES AND PATIENTS' AGES; AND EFFECT ON BODY-WEIGHT IN CASES WELL CONTROLLED BY CHLORPROPAMIDE

Type of diabetes	Control on chlorpropamide				Effect on body-weight in cases with good control					
	Satisfactory		Poor		No effect	Gain		Loss		Total average (lb.)
	Duration (yr.)	Age (yr.)	Duration (yr.)	Age (yr.)		No. of patients	Average (lb.)	No. of patients	Average (lb.)	
Mild onset, no insulin	<1–17	35–81	<1–24	43–83	7	22	2·9	13	3·8	+0·33
Less than 40 units insulin per day	1–24	54–84	1–27	52–78	8	17	2·2	10	3·5	+0·05
More than 40 units insulin per day	4–20	52–75	4–12	29–68	3	2	3·5	1	1·0	+1·0
Acute ketotic onset	1–20	55–74	<1–11	33–71	1	3	2·7	2	1·5	+0·83
Total averages	8·1	63·9	7·2	60·7	..	..	2·8	..	2·5	+0·55

on the response to this compound. It must be appreciated in assessing these figures that no cases treated with chlorpropamide immediately after diagnosis are included unless it had been demonstrated that diet alone failed to produce good control. We have, however, administered chlorpropamide to many patients immediately after diagnosis and found it extremely effective at this stage in producing rapid relief of symptoms and satisfactory diabetic control.

Chlorpropamide produced an average gain in weight of 0·55 lb. in those patients who were satisfactorily controlled (table II).

Of the 25 patients who failed to respond in the first two groups shown in table I, 6 showed some response on 250 mg. per day but never received a higher dosage and a further 7 received a low initial dosage of 200 mg. or less per day. These were some of the first patients treated in this series when various dosage schemes were being tried. We found with experience that the most effective was an initial dose of 250 or 375 mg. reducing to 200 mg. per day. In our opinion there is no advantage in exceeding 250 mg. per day once good control has been achieved.

The maximum period of treatment of any patient in this series is 7 months, and so far only 5 cases have relapsed after a period of good control on chlorpropamide. Of these, 2 were young ketotic diabetics aged 32 and 34 years, who were started on the drug during the period of increased carbohydrate tolerance which often follows the institution of insulin therapy, and the 3 other cases were complicated by some unrelated medical condition.

In addition, both tolbutamide and chlorpropamide have been used in the treatment and suppression of steroid-induced diabetes. 1 patient included in the present series was successfully converted from 60 units insulin zinc suspension per day to chlorpropamide. It is now our practice to administer either tolbutamide or chlorpropamide to all patients at the onset of steroid diabetes. It is too soon to analyse our results completely, but even with the continuation of steroid therapy the 5 cases treated have all reverted to normal carbohydrate tolerance within 7 days. All cases have been shown to relapse without treatment. 1 of these cases is now receiving the equivalent of 800 mg. cortisone per day.

Discussion

On the above evidence chlorpropamide is the most effective sulphonyl urea at present available. It has a greater range of activity than tolbutamide, and so far we have not detected any case which is resistant to chlorpropamide and responsive to tolbutamide. The incidence of toxic effects is low when the maximum dosage is limited to 375 mg. per day. In other reported trials of this compound (Hamff et al. 1959, Canessa et al. 1959) impairment of hepatic function has been detected in a few cases 2–3 weeks after the start of treatment. In nearly all these cases the dosage exceeded 375 mg. per day and it was found that these patients could be well controlled on a lower dose with no demonstrable impairment of hepatic function (Hamff et al. 1959). Transient reversible leucopenia, eosinophilia, lymphocytosis, intolerance to alcohol (Serrano and Chavez 1959) and neuropsychiatric disturbances (Murray et al. 1958) have also been reported. When the maximum dose is limited to 375 mg. per day these effects did not occur in our series, and we have found that very little improvement in diabetic control can be achieved by exceeding this dosage.

When replacing insulin by chlorpropamide gradual substitution is more successful and safer than sudden stoppage (Nabarro 1959).

Although we based our evidence of control on the morning urine and noon blood-sugar it was seen with patients in hospital that the daily glucose output was much less on chlorpropamide than on small doses of the long-acting insulins. This was particularly noticeable in the late evening specimen of urine, which is usually sugar-free on chlorpropamide but contains 0·5–1 g. sugar per 100 ml. with good control on a long-acting insulin.

Some of the cases which have shown a partial or temporary response have been treated by the addition of aspirin with a good response (H. Keen, personal communication). A similar effect has been reported by Stowers et al. (1959).

No change was made in the daily ration of carbohydrate or its distribution at the various meals in patients receiving chlorpropamide. Since completing this trial we have adopted a dietary regime similar to that recommended for the insulin zinc suspensions (Gurling et al. 1955) except that only 10 or 20 g. of carbohydrate is allowed for afternoon tea and more laxity is permitted with mealtimes.

It has been suggested that the sulphonyl ureas act by stimulating the production of insulin (Loubatieres 1957); and with this in mind, in cases where diabetes has been detected by routine testing before the onset of symptoms and ketosis, we have administered both tolbutamide and chlorpropamide to adolescents and children. The results in the few cases treated have been sufficiently good to encourage us to expand this work and explore the possible value of these compounds in delaying the onset of classical juvenile diabetes at this age.

Summary

Chlorpropamide was given to 126 diabetic patients, and in 89 satisfactory diabetic control was produced.

Chlorpropamide has a greater range of activity than tolbutamide and is effective in cases which relapse on tolbutamide therapy. The incidence of toxic effects is low when the maximum dose does not exceed 375 mg. daily. The patient's age and the duration of diabetes had no bearing on the response to chlorpropamide in this series.

Preliminary results suggest that steroid-induced diabetes can be suppressed by the administration of either tolbutamide or chlorpropamide in the early stages of the disease.

We wish to acknowledge the considerable help we have received from Sister Maureen Tomlinson and the medical, technical, and administrative staff of the Diabetic Department.

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THROMBOTEST

A NEW METHOD FOR CONTROLLING ANTICOAGULANT THERAPY

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DURING the past ten years short-term anticoagulant treatment of thromboembolic disorders has become firmly established. Long-term anticoagulant treatment has gained ground slowly but steadily. Careful studies by Waaler (1957), Bjerkelund (1957), and recently by the Medical Research Council (1959) have demonstrated that many patients benefit from such treatment. Henceforward it will be given increasingly.

At present, however, there are two problems connected with its use on a larger scale. The first is the safety of the treatment: the patients must be protected from bleeding. The second is its feasibility: the present methods of control are difficult, expensive, and time-consuming. Centralisation of control has been necessary in most places, and only a limited number of patients can be supervised.

In our laboratory a new method has been specifically devised to overcome these obstacles. The method may also be used for the clinical study of liver diseases and the conditions produced by vitamin-K deficiency.

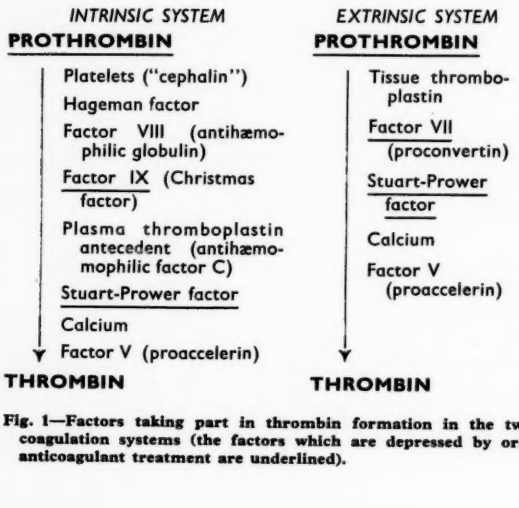

Fig. 1—Factors taking part in thrombin formation in the two coagulation systems (the factors which are depressed by oral anticoagulant treatment are underlined).

Method

Principle

Normal clotting of blood occurs through two partly separate systems called the "intrinsic" and the "extrinsic" coagulation systems (fig. 1). The clotting factors of the first system are all present in circulating blood. Coagulation is initiated by contact with a foreign surface and takes several minutes, depending on the type of surface. The extrinsic system is initiated by tissue fluid containing thromboplastin. In the presence of an active tissue thromboplastin, blood clots in only 12–15 seconds, and thus the activity of the slower intrinsic system cannot be detected.

During treatment with dicoumarol-like drugs, both the intrinsic and the extrinsic coagulation systems are depressed, the former through reduction of factor IX (Christmas factor), the latter through reduction of factor VII (proconvertin). Reduction of the Stuart-Prower factor and prothrombin influences both systems. The new method is based on the principle that adequate control should include a combined determination of all four factors which are depressed by the anticoagulant treatment. The test has therefore been so designed that it is equally sensitive to both coagulation systems. This has been achieved by adjusting the two systems so that they operate at about the same speed during the test. The intrinsic system has been accelerated by the introduction of an active cephalin preparation, while the extrinsic system has been retarded by the introduction to a thromboplastin of low activity.

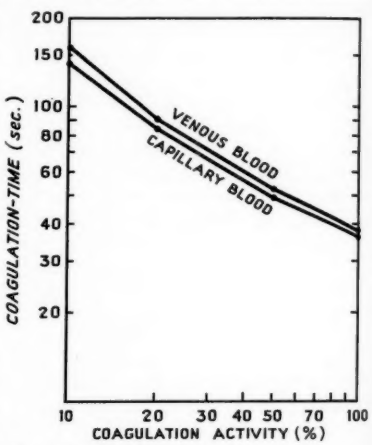

Fig. 2—Correlation curve for converting clotting-times to coagulation activity (% of normal).

For maximum simplicity an "all-in-one-reagent" has been devised. It contains the cephalin, the thromboplastin, and a substrate-plasma with a high and constant content of all clotting factors which are not influenced by anticoagulant treatment. The plasma has been completely freed of the four factors to be determined. When the patient's blood or plasma is added to this reagent, the clotting-time will depend only on the concentration of these four factors in his blood.

The Reagent

The "all-in-one-reagent"* has the following four components:

1. "*Crude cephalin*" is prepared by ether extraction of human brain or soya bean. It has a high activity towards human plasma, and is adjusted to optimal concentration, giving a "cephalin-time" with human plasma of 40–50 seconds.

2. *Thromboplastin* is prepared from animal organs—for instance, ox or horse brain. It has low reactivity with human

* The thrombotest reagent is available from Nyegaard & Co., Nycoveien, Oslo, Norway.

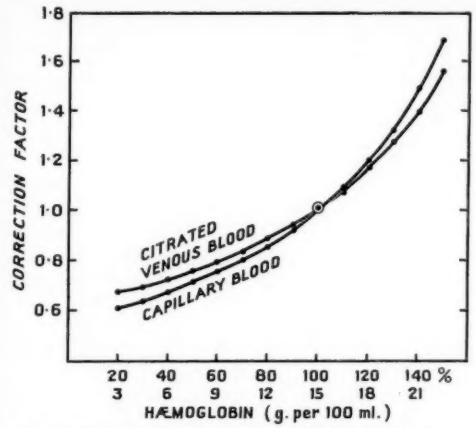

Fig. 3—Correction chart for abnormal hæmoglobin values.

factor VII because of the pronounced species specificity of the thromboplastin/factor-VII reaction. With this thromboplastin in optimal concentration the thromboplastin-time with human plasma is 35–45 seconds, a time which provides good balance between the two clotting systems.

3. *Adsorbed bovine plasma* has been freed completely of the four factors concerned, while it contains all other clotting factors in suitable concentrations. The pH of the plasma is stabilised at 7·3.

4. *Calcium chloride* is added in optimal concentration.

The four ingredients are mixed in one reagent which is lyophilised and kept in vacuum-sealed ampoules. It is reconstituted with distilled water for testing of capillary blood, and with a weak calcium chloride solution (3·2 mM) for testing of citrated blood or plasma. The final reagent is opaque because cephalin and thromboplastin are insoluble in aqueous media and form a fine suspension.

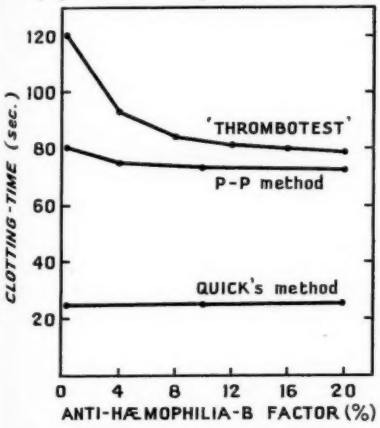

Fig. 4—Sensitivity to factor IX (Christmas factor).

Plasma from a patient with Christmas disease was mixed with normal plasma in various proportions. The mixtures were assayed in three test systems after dilution 1/4 with adsorbed human plasma to imitate conditions during anticoagulant therapy (concentrations of prothrombin, factor VII, and Stuart-Prower factor about 20% in all samples tested).

Lyophilised and vacuum-sealed, the reagent will keep for 12 months at room temperature; the activity is unchanged after storage for 30 days at 47°C. After reconstitution the activity is constant for 12 hours at room temperature and for 3 days at 6°C. If the reagent is stored overnight in the icebox, it should be well mixed before further use.

Equipment

1. Pipettes for measurement of (*a*) solvent, 11 ml. or 2·2 ml.; (*b*) reagent, 0·5 ml. ; (*c*) blood, 0·1 ml. Standardised pipettes with a length of 8–10 cm. are preferred.†

2. Small test-tubes with an inner diameter of about 8 mm. and length of 5–6 cm.

3. Water-bath at 37°C.

4. Stop-watch.

5. For capillary blood, sharp blade ('Gillette' surgical blades, shape E, are suitable). For venous blood, 2 ml. syringe.

Method for Capillary Blood

The lyophilised reagent is dissolved in distilled water. The specified volume must be accurately measured by means of a pipette and allowed to run down the inside of the ampoule. The contents are shaken gently to avoid froth formation. Solution occurs in 1–2 minutes.

0·5 ml. of the reagent is measured into a small test-tube and left in the water-bath at 37°C for a minimum of 3 and a maximum of 30 minutes, to reach the correct temperature. After cleaning the skin with ether, an incision or puncture is made in the ear-lobe or the tip of the finger with a sharp blade. 0·1 ml. of capillary blood is aspirated into a pipette and immediately transferred to the small test-tube and mixed with the reagent. A stop-watch is used to measure the coagulation-time, which is taken as the time between addition of the blood to the reagent and the formation of a solid clot. The appearance of a clot is almost instantaneous, and the end-point is easily determined. The coagulation-time is converted to coagulation activity, expressed as a percentage of the normal, with the aid of a correlation curve (fig. 2).

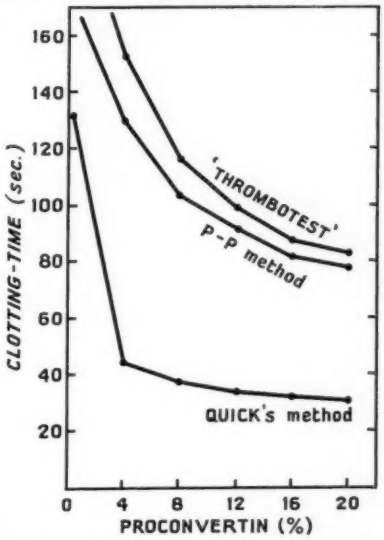

Fig. 5—Sensitivity to factor VII (proconvertin).

Plasma from a patient with congenital deficiency of factor VII was mixed with normal plasma in various proportions. The mixtures were assayed in three test systems after dilution 1/4 as described in fig. 4.

Method for Venous Blood

Citrated blood with 1 volume of 3·13% (w/v) sodium citrate dihydrate to 9 volumes of blood is used. When used for citrated blood, the lyophilised reagent must be dissolved in a calcium-chloride solution of 3·2 mM that accurately compensates for the citrate in the blood sample.

The blood specimen is best taken with a syringe. 0·2 ml. of the citrate solution is accurately measured into a 2 ml. syringe, blood is aspirated to a total volume of 2 ml., and the mixture is transferred to a small test-tube ('Lusteroid',‡ plastic, or siliconised glass tube in order to prevent contact activation, see below). A 0·1 ml. aliquot of this citrated blood is aspirated into a pipette and mixed with 0·5 ml. of the reagent, and the coagulation-time is determined. The coagulation activity in per cent. is read from a correlation curve for venous blood (fig. 2).

† These can be obtained from H. J. Elliot Ltd., Treforest Industrial Estate, Glamorgan, Wales.

‡ Lusteroid tubes can be obtained from Lusteroid Container Co. Inc., Maplewood, New Jersey, U.S.A.

Method for Citrated Plasma

Citrated blood is centrifuged and a measured volume of plasma is diluted with normal saline in the proportion 3/2 (for example, 0·6 ml. of citrated plasma and 0·4 ml. of saline are mixed in a small test-tube). Tubes which prevent contact activation must be used. 0·1 ml. of the diluted plasma is added to 0·5 ml. of the reagent and the clotting-time estimated as described. Coagulation activity in per cent is read from the same curve as for venous blood.

Preparation of the Correlation Curve

The correlation curve for venous blood, and citrated plasma in dilution 3/2, is prepared by testing serial dilutions in normal

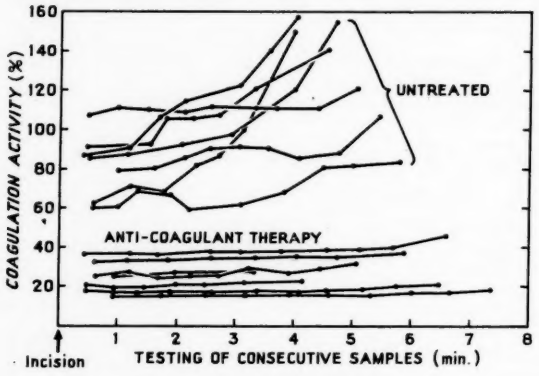

Fig. 6—Testing of capillary blood.

Consecutive drops from the same wound were tested immediately upon withdrawal. The abscissa gives time after the incision.

adsorbed plasma of a normal standard reference plasma. This is obtained by pooling plasma prepared from 5 male donors with normal hæmatocrit (43–47) using silicone technique. It is stored in aliquots in stoppered lusteroid or siliconised tubes at −25°C. The serial dilutions are again diluted 3/2 with normal saline before being tested, because the correlation curve refers to whole citrated blood. (The volume of red cells is substituted by saline.)

The correlation curve for capillary blood is constructed at a 10% lower level, as the test sample of capillary blood contains 10% more plasma than citrated blood. Serial dilutions of normal capillary blood using silicone technique have given identical curves. The curves are drawn on log graph paper (see fig. 2). Standard curves are made for each production batch and supplied with the dried reagent. The use of a standard dilution curve is made possible by the high stability of the reagent. It provides a means of comparing results from different laboratories.

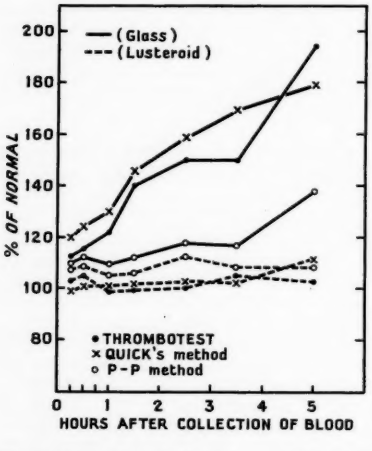

Fig. 7—Activation of citrated venous blood on storage in glass tubes.

Comparison of the thrombotest, the P & P method, and Quick's method. No activation takes place during 5 hours in lusteroid tubes.

Quick's method showed a reduction from 14·8 sec. to 12·6 sec. in 5 hours. These values have been translated to percentage, for comparison, by extension of the correlation curve above 100%.

Correction for Abnormal Hæmatocrit

The coagulation activity should always be given as a percentage of the activity of normal plasma. When capillary or venous whole blood is tested, the quantity of plasma in the test sample depends on the hæmatocrit: in anæmia the quantity will be above normal, in polycythæmia below normal. With marked deviations from normal the percentage value read from the correlation curve should be corrected, but it is rarely necessary in anticoagulant therapy. A chart (such as fig. 3) makes this correction easier.

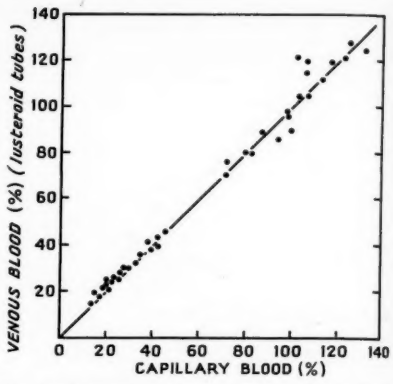

Fig. 8—Comparison of % activity as determined with the capillary method and the venous method.

Two samples were taken from each subject; capillary blood was drawn into a non-siliconised pipette; venous blood was drawn through a siliconised needle into a lusteroid tube.

The Test in Practice

Sensitivity

The clotting system has been so adjusted that the coagulation-times are short enough to permit sharp clot formation (thus aiding accurate reading), but on the other hand long enough to give relatively large variations in clotting-time with small variations in percentage activity. This is an important practical point, since a technical error of 1–2 seconds in the reading will not cause a large deviation in the calculated percentage activity. Clotting-times for samples during anticoagulant therapy in the therapeutic range of 10–30% vary from about 50 to about 100 seconds. Hence little training is required to obtain reliable results.

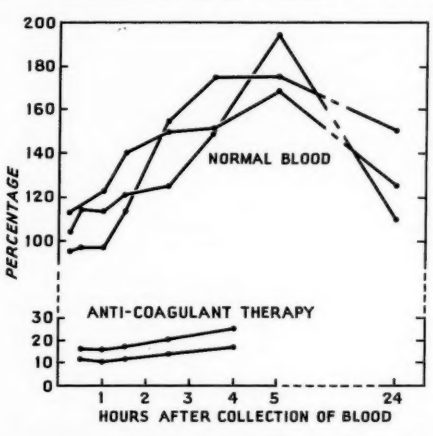

Fig. 9—Activation of citrated blood in glass tubes (the "activation product" is subsequently inactivated).

The method is sensitive to variations in factor IX, in contrast to the complete absence of sensitivity of Quick's

method and the slight sensitivity of the P & P method to this factor (fig. 4).

The sensitivity to factor VII is illustrated in fig. 5.

The sensitivity to parallel reductions in all four factors was studied by mixing adsorbed and normal plasma in various proportions. The curve was similar to the correlation curve (fig. 2).

Therapeutic Range

The therapeutic range for anticoagulant therapy as controlled by this method is considered to be 10–30% of normal. The lower level is determined by the risk of bleeding, the upper level by the risk of inadequate therapy. The upper level must be determined by clinical experiments, but precise information is so far not available on this point. Such a study is under way in our laboratory.

Sources of Error

Coagulation in Capillary Blood

If appreciable coagulation is allowed to start in the capillary (non-citrated) blood before it is tested, inter-

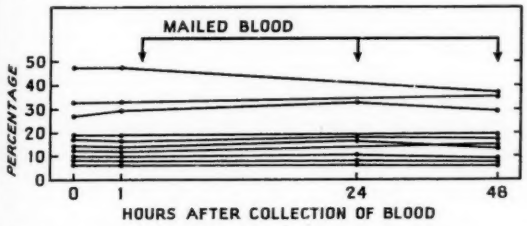

Fig. 10—Stability of blood samples sent by post in lusteroid tubes (patients on anticoagulant therapy).

mediate products will form, giving accelerated clotting-times. When consecutive drops of blood from one puncture in normal subjects were tested, acceleration was observed after 1–2 minutes (fig. 6). Blood from the first drops should therefore be used for the test.

When the same experiment was performed in patients on anticoagulant treatment, acceleration was not observed until about 5 minutes after the puncture (fig. 6). The same lack of acceleration was found in patients with congenital clotting defects, even those not involving the four factors which are depressed by anticoagulant treatment.

Contact Activation of the Test Sample

Contact of blood or plasma with glass initiates activa-

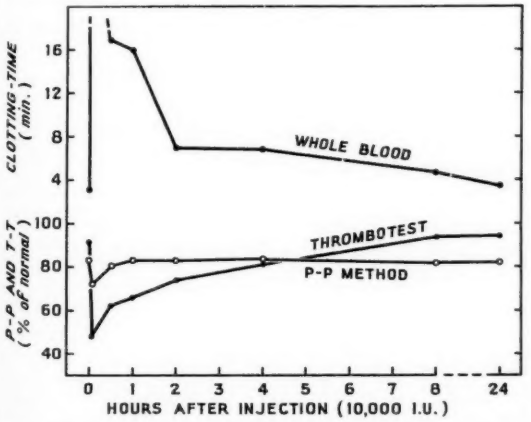

Fig. 11—The effect of heparin on the whole blood clotting-time, the P & P test, and the thrombotest.

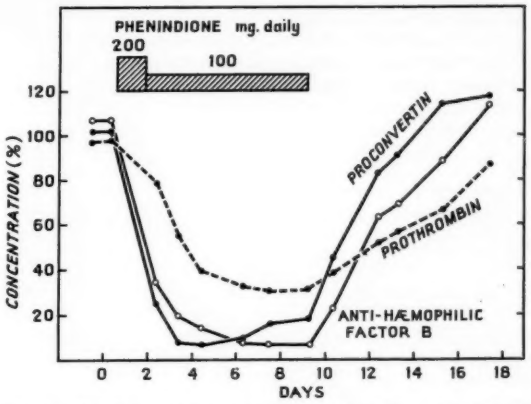

Fig. 12—The clotting defect induced by phenindione. The Stuart factor was not measured in this experiment.

tion processes which accelerate both clotting systems. In the intrinsic system a reaction is initiated between the Hageman-factor and plasma thromboplastin antecedent (antihæmophilia-C-factor) with formation of an " activation product " (see Waaler [1959] for review). In the extrinsic system factor VII appears to become activated. These activation processes are independent of calcium and therefore take place even in citrated plasma. All methods, therefore, give false high values by the testing of venous blood stored in glass (fig. 7). Activation may

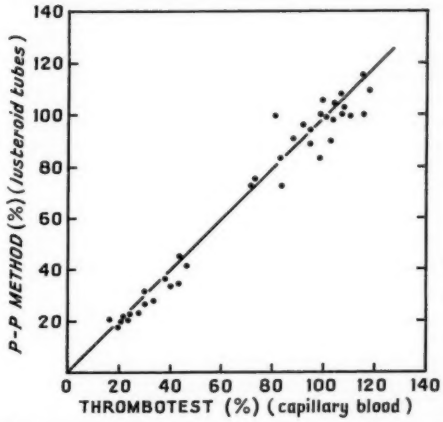

Fig. 13—The correlation between the P & P test and the thrombotest.
Two samples were taken from each subject. Capillary blood for thrombotest was drawn into a non-siliconised pipette; venous blood for the P & P test was drawn through a siliconised needle into a lusteroid tube.

be prevented by the use of siliconised glass, lusteroid, or plastic tubes.

In the method for capillary blood, contact activation does not occur when the blood is in the pipette—probably because the time is too short. Thus the results obtained by the capillary method using non-siliconised pipettes correspond precisely to the results obtained using venous blood collected in lusteroid tubes (fig. 8).

On the other hand, with the method for venous blood and citrated plasma contact activation is important as a source of falsely high values. If the blood is allowed to stand in ordinary glass tubes rapid activation takes place, especially of normal blood (fig. 9). Therefore, unless the

blood is tested immediately after withdrawal, it should always be collected in lusteroid, plastic, or siliconised tubes. The contact activation is then prevented for 2 days, and blood from patients on anticoagulant therapy may be sent to the laboratory by post for testing (fig. 10). If such blood is tested within an hour of withdrawal, however, glass tubes may be used (fig. 10).

Inactivation of Clotting Factors

When oxalated or citrated blood or plasma is stored for some hours, factor V (proaccelerin) and factor VIII (anti-hæmophilic-globulin) are inactivated. The thromboplastin-time and the " cephalin-time " become prolonged. This inactivation does not influence the new method, because the reagent contains both factor V and factor VIII in high and stable concentration. It should be emphasised, however, that no sample should be stored for more than 2 days.

Non-optimal Calcium Concentration

The citrate (oxalate) concentration of plasma will vary depending on the hæmatocrit. It is high in polycythæmia and low in anæmia. When a constant amount of calcium is added to undiluted plasma for recalcification, as for instance in Quick's test, the resulting calcium concentration during coagulation will vary and become non-optimal in anæmia and polycythæmia. This source of error is eliminated in the new method when capillary blood or citrated venous blood is used.

Influence of Heparin

Sometimes it is necessary to start anticoagulant treatment with both heparin and an oral anticoagulant. It is important, therefore, to know the extent to which the test is influenced by heparin. Fig. 11 shows that the test cannot be used to measure the effect of an oral anticoagulant until at least 8 hours after the intravenous injection of an average dose of heparin. The P & P test is less sensitive to heparin, since in this case plasma is tested in a 1/10 dilution.

Discussion

A number of tests may be used in the control of anticoagulant treatment. With care and skill good results may be obtained with many of them. The problem is not, therefore, whether a test can be used for the control of anticoagulant treatment, but to devise the best test possible. Such a test should be theoretically adequate—that is, it should reflect the total defect induced in the patient's clotting system (see fig. 12). It is equally important, however, that it should be both simple and reliable, even in the hands of technicians who are not trained in coagulation techniques. Most tests previously used have not fulfilled these criteria.

Mayer and Connell (1957) controlled their patients with the whole-blood clotting-time, aiming at a time of 15–22 minutes (normal about 10). This method measures only the activity of the intrinsic system; it is influenced by factors which are not reduced by anticoagulant treatment; and each test takes too long a time. Recalcification-time has the same disadvantages as the whole blood clotting-time.

Thrombelastography (Loeliger 1958) also reflects only the intrinsic system. It is influenced by factors not reduced by anticoagulant treatment; expertly-drawn venous blood must be used; an expensive machine is necessary; and the capacity of the machine is small.

The use of the heparin-tolerance test is advocated by Soulier et al. (1951), Marbet and Winterstein (1955), and Loeliger (1958). Again, the test is sensitive only to the intrinsic system, and it is influenced by factors not reduced by anticoagulant treatment, such as platelets. Fresh blood must be used, and considerable technical skill is necessary.

Quick's thromboplastin-time reflects the extrinsic system, including factor V and fibrinogen. Experience has shown that this test may be successfully used to control anticoagulant therapy, but in our opinion it is not ideal for this purpose. It requires experience and skill, since the clotting-times are short, particularly in the 50–100% range. Furthermore the quality of the thromboplastin is of decisive importance, and different thromboplastins may give widely differing results for the same test plasma.

The P & P method was designed to overcome some of the criticisms of Quick's method. It is not sensitive to changes in proaccelerin and fibrinogen, and it requires less skill. In our laboratory the method has been far more reliable than the thromboplastin-time, and we think it is better suited for the control of anticoagulant therapy. During the past 10 years we have used it extensively on outpatients on permanent anticoagulant treatment. Practical experience has shown that such patients can be maintained in the 10–30% range for years without significant risk of bleeding. Nevertheless, the P & P method cannot be considered the final solution to the problem. It has the theoretical disadvantage of not being sensitive to the intrinsic system, and it is not simple enough.

The thrombotest is the only method which is sensitive to changes in both clotting systems. It is difficult to know how important this is. During anticoagulant therapy there is often a poor correlation between the Quick test and specific tests for the intrinsic system (Loeliger 1958); but, on the other hand, we have found a good correlation between the P & P test and the thrombotest if venous blood is collected in lusteroid or siliconised tubes (fig. 13). If venous blood for the P & P test is stored in glass tubes, activation also influences this method (fig. 7). We think that in most patients the induced defect in the intrinsic system parallels that in the extrinsic system. Nevertheless bleeding may occur if factor IX is disproportionately reduced in a patient who is controlled by an " extrinsic " test, and the new test therefore increases the safety of the treatment. In addition, the new method is simpler than any other method, because of the lyophilised " all-in-one-reagent ", and because capillary blood can be used.

Summary

1. This new method for the control of anticoagulant therapy differs in principle from earlier methods by measuring the coagulation activity of the adsorbable factors in both the intrinsic and extrinsic coagulation systems; thus it is sensitive to depression of factor IX (Christmas factor) during anticoagulant therapy.

2. Only one reagent is used, which is stable both in lyophilised form and after reconstitution.

3. The method needs little equipment and the technique is simple. Little experience is required to obtain a reliable result, which is known in 2–3 minutes.

4. The method has been worked out with capillary blood in mind, but it can also be used for citrated venous blood, and citrated plasma if precautions are taken to avoid activation by contact.

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PARTIAL NEPHRECTOMY
A CRITICAL STUDY

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UNTIL the advent of the antituberculous drugs the standard treatment of renal tuberculosis was nephrectomy as early as possible. This radical treatment—although accepted as the best available at the time—was often unsuccessful; and over 20% of patients were dead within five years. In 13·3%, moreover, the operation wound broke down and continued to discharge for a long time, in some cases leading to amyloid disease (British Association of Urological Surgeons 1953).

Since the introduction of *p*-aminosalicylic acid (P.A.S.), streptomycin, and isoniazid, the treatment and outlook of genitourinary as indeed of all forms of tuberculosis has changed. In 1953 Semb introduced the selective principle into the treatment of renal tuberculosis, advocating segmental resection of the diseased or destroyed part of the kidney. In this paper we shall examine a series of patients who have undergone partial nephrectomy in the Genito-Urinary Unit at Wrightington Hospital since 1952. All have been seen recently, and it is our intention to follow up as many as possible annually for a period of ten years.

Material

37 partial resections were performed—9 in women and 28 in men (see table). The upper pole was excised in 20 and the lower in 17, no resection of the middle segment being carried out. Complications were very few. 5 patients had hæmaturia which subsided in all cases by the seventh day. 2 had a urinary leak which ceased after ten days and six weeks respectively. 1 patient died from coronary thrombosis twenty-four hours after operation.

DATA ON 552 PATIENTS TREATED FOR GENITOURINARY TUBERCULOSIS IN 1952–58

Year	No. of partial nephrectomies	Total no. of patients
1952	5	72
1953	4	90
1954	7	83
1955	7	104
1956	13	83
1957	1	62
1958	0	58

The table shows that after the peak in 1956 only 1 partial nephrectomy was performed in 1957 and none in 1958. This indicates a trend towards a more conservative regime, the result of success with antituberculous drugs.

Treatment

The three essential and inseparable components of treatment are a sanatorium regime, chemotherapy, and elective surgery. We feel convinced that each component is important and that the best results can be achieved only by the proper integration of the three.

For the operation of partial nephrectomy we use the normal lumbar approach, removing the twelfth rib in most cases.

After exposure of the kidney the sinus is carefully dissected, and vessels supplying the pole are ligated in continuity. The capsule is incised over the convexity of the affected pole, and anterior and posterior capsular flaps are reflected back beyond the proposed level of section. The main vessels are clamped, care being taken not to leave the clamp in situ for longer than fifteen to twenty minutes. A V-shaped excision of the diseased part is performed and the neck of the calyx is sutured with fine plain catgut. The clamp is released and the bleeding-points are ligated. The reflected capsule is now placed over the kidney defect and usually provides a double layer. A few interrupted sutures are placed through it, taking in some kidney substance to approximate the lips of the V-shaped defect. The last stage is suture of the capsule by a continuous fine catgut stitch. If a satisfactory V-shaped excision cannot be made and closure is difficult, a graft of fat or muscle is placed into the defect. Finally, the kidney is sutured to the posterior abdominal wall and suspended by a sling constructed from the fascia of Gerota and the quadratus lumborum. The wound may or may not be closed without drainage—usually the former.

We do not subscribe to the views recently expressed by Power (1958) that a simplified procedure based on a guillotine-type amputation is safe.

Results

Clinical progress, the histopathology of the resected part, and radiological findings have been studied.

Clinical progress

Of the 36 patients who survived 26 have remained well, with a sterile urine, for two to six years. The urine of 2 patients remained positive after partial nephrectomy, and although there has been no radiological deterioration 1 of them still excretes tubercle bacilli five years later. The urines of 3 patients reverted to positive within six months to a year, and of 5 others within one to two years. In the whole series therefore, 10 patients (27%) remained or reverted to positive within two years of the operation, although the clinical condition remained excellent.

In none of the 14 patients operated on since 1956 has the urine reverted to positive. This may be due to more efficient treatment since it was about this time that we lengthened the period of post-sanatorium chemotherapy from three months to a year.

The 2 patients whose urines remained positive after partial nephrectomy showed active disease in the excised renal tissue; whereas of the 8 who reverted some time after operation 7 had an inactive lesion or no evidence of tuberculosis in the resected specimen.

Inadequate excision may account for a persistently positive urine. Delayed reversions to positive, with inactivity or no lesion in the specimens, may be explained by failure to isolate the organisms from the urine for a time after operation, or by active foci left behind in the remaining kidney segments or in the contralateral kidney.

All cultures and inoculations are made from early-morning urines: we have found that this produces the highest percentage of positives (Ross 1955). Unfortunately, it is impossible to determine which kidney excretes the organisms, or even whether they emanate from a focus in the prostate or seminal vesicles. We no longer collect specimens by retrograde catheterisation: only 17 positive urines were obtained in 334 such examinations and we are reluctant to subject the patient to this investigation when the intravenous pyelogram is satisfactory.

Histopathology

All resected renal tissue was submitted to histopathological examination in order to determine the adequacy of the resection and to assess the activity of the disease. We have classified the lesions into three grades.

1. *Active lesions* show a cellular tuberculous inflammatory reaction, with or without caseation, and little or no fibrous tissue in the periphery.

2. *Moderately active lesions* are surrounded by considerable fibroblastic and fibrous tissue, but have either tuberculous foci within the fibrous boundary or scattered microscopic foci immediately outside it.

3. *Quiescent* lesions are surrounded by dense fibrous tissue with little or no inflammatory reaction and no recognisable tuberculous foci.

In this series of specimens 6 lesions were active, 4 moderately active and 27 quiescent. Lesions with large cavities did not necessarily show great activity; in fact 2 of the smallest cavities proved to be the most active. This suggests that there is no need to operate at an early stage merely because the patient has a large cavity: such cavities are just as likely to become quiescent under efficient chemotherapy as smaller ones.

Radiological Findings

All cases were first investigated by intravenous pyelography. When a calyceal deformity was found, or when the calyces were inadequately shown, a retrograde pyelogram was performed, with both straight and oblique views. We have as yet seen no case of dramatic pyelographic improvement—i.e., calyceal patterns deformed by ulcerocavernous lesions becoming normal after chemotherapy. This is only to be expected; since, even when the disease becomes quiescent and cavities acquire an epithelial lining (shown by a smoother radiological outline) there is no regeneration of renal tissue. One should therefore distinguish between "radiological improvement" and "restoration to normal".

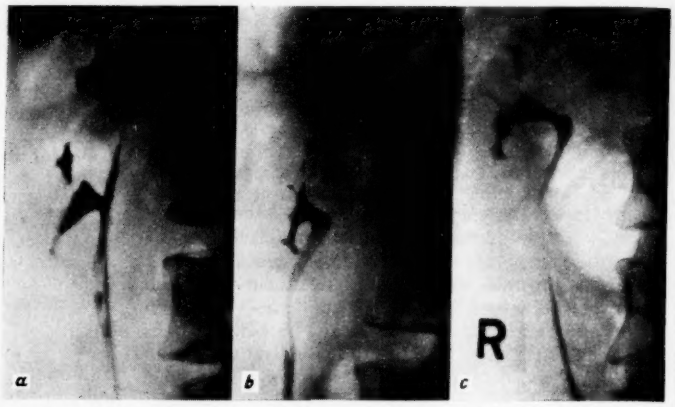

Fig. 2—30-minute intravenous pyelograms, showing (*a*) tuberculous disease of the upper pole of a duplex kidney; and (*b* and *c*) a well-functioning lower pole with a small stump of ureter after partial nephrectomy.

Only 3 out of over 700 cases of genitourinary tuberculosis treated in this unit during the past ten years have shown any radiological improvement, and none of the 3 were in the present series.

The size of the cavities varies widely and apparently bears no relationship to the presence or absence of organisms in the urine. The results of culture and guineapig inoculation are more important than the X-ray appearances.

Discussion

Although this is a small series, it is possible to draw from it support for a more conservative attitude to renal tuberculosis. The wheel of progress has thus turned almost a full circle. Immediately before and after 1952 the tendency was to resort to surgery earlier and more frequently: now it is becoming less and less necessary, the indications being few though definite. We believe that many cases which were treated in the past by polar nephrectomy would now be treated successfully by protracted chemotherapy under sanatorium conditions; and we strongly oppose operative interference in patients with a single kidney.

What then are the indications for partial nephrectomy? Semb (1957) believes that operation should still be carried out on a considerable number of patients, whereas Lattimer and Spirik (1956) claim that extirpative surgery is no longer necessary and state that they have not performed a partial or a total nephrectomy for three years. Hanley (1957) advocates surgery to drain closed calyceal lesions and to excise cavernous areas. Cibert (1957) considers that the only indication for partial nephrectomy in the treatment of renal tuberculosis is a closed cavity (causing renal colic or pain) at one or other pole. May (1956 a and b) advocates a more radical policy; he performs partial nephrectomy in cases of extensive cavitation of long duration, when the urine remains positive despite protracted conservative treatment, or when a cavity is shut off or a calyceal neck stenosed.

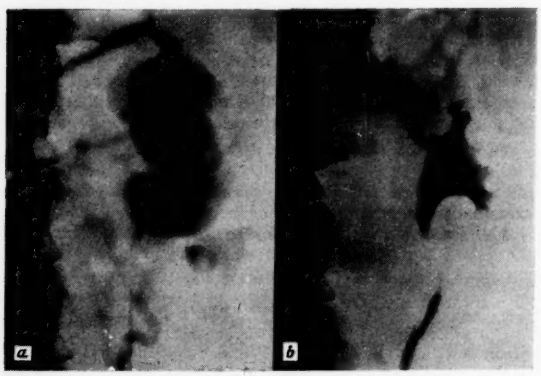

Fig. 1—Retrograde pyelogram, showing (*a*) gross tuberculous disease of the upper pole of a duplex kidney; and (*b*) a 30-minute intravenous pyelogram, showing good function in the lower pole after partial nephrectomy.

As a result of the present investigation we believe that a sterile urine is more important than the radiological findings, and that surgery should not be contemplated if organisms cannot be isolated. As the resected specimens of 27 of our patients contained inactive lesions, the trend must clearly be towards conservatism, and partial nephrectomy should be considered only when a cavity persistently secretes tubercle bacilli despite protracted chemotherapy. Such a situation may arise because organisms become resistant to chemotherapeutic agents, because a patient's resistance is low or because of other, unknown, factors. In the present state of our knowledge we do not feel that lesions which have become shut off at the calyceal neck should necessarily be excised: out of 7 such cases in this series the disease was inactive in 5. We believe, however, that there is a second indication for operation. When the upper or lower pole of a duplex kidney and its ureter is diseased (and the other part is normal), the affected half should be excised in order to prevent the common ureter from becoming involved and from endangering the function of the other half of the kidney. There were 2 such cases in this series, and the results are illustrated in figs. 1 and 2.

Summary

37 patients who had undergone partial nephrectomy have been studied.

Our results suggest that the treatment of genitourinary tuberculosis should be more conservative. Neither a large renal lesion nor a calyx which has been sealed off is necessarily an indication for operation.

The most important indication for surgery is a persistently positive urine.

The operation requires a careful technique and meticulous hæmostasis.

We should like to thank Mr. C. R. Helsby for his help in the preparation of this paper.

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FORTY-SIX CHROMOSOMES IN AN OVARIAN TERATOMA

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THE problem of the origin of teratomas has been reopened by the assignment of nuclear sex using the Barr chromatin technique. The results of these investigations have been summarised by Moore and Barr (1957) and by Ruge (1958). In the relatively few teratomas reviewed by these authors (to which several other studies should now be added—e.g., Ashley and Theiss 1958) it has been found that nuclear chromatin is present in about half the tumours of male origin, while all except Brüning (1956) found a positive chromatin pattern in all teratomas of females. To most investigators this indicates that these tumours are of gametal origin. Whether this is by conjugation of gametes or by parthenogenesis of a single haploid cell with chromosome reduplication remains to be elucidated. But the finding of two primary extragenital chromatin-positive teratomas in genetic males (Hunter and Lennox 1954, Cruickshank 1955) strongly suggests the latter possibility.

While the histology and the frequent presence of sex chromatin favour the diploid chromosomal constitution of teratomas, only actual chromosome-counts will reveal the ultimate genesis of these tumours. The anticipated removal of a metastatic teratoma in one of our patients made it possible to attempt the first chromosome-count of such a tumour.

Method

The tissue for this study was obtained at the third operation on a recurrent, solid, well-differentiated teratoma from a 24-year-old woman, whose original tumour in the left ovary followed her only pregnancy 2 years previously. The clinical and pathological findings in this patient and two others with these unusual tumours are described in detail elsewhere (Benirschke et al. 1959).

Successful explants were obtained from a large solid metastasis to the colon. 1 mm. cubes were cultured in vitro,

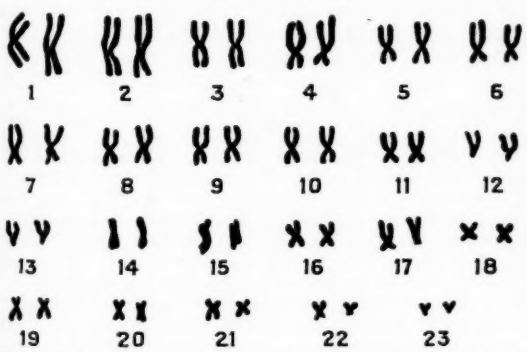

Fig. 1—Forty-six chromosomes charted according to size, the XX pair presumably being no. 7.

Fig. 2—" Plate " showing squashed metaphase and adjacent nucleus with Barr chromatin body. Slightly different focus and photography allow accurate charting of chromosomes. (Feulgen. ×1800.)

Fig. 3—Metastasis of tumour used for tissue culture. An admixture of well-differentiated tissues (cartilage, mucosa, fat, skin, glia, &c.) is present. (Hæmatoxylin and eosin. ×55.)

employing the method used by Hellweg and Shaka (1959). Colchicine was added (final concentration 10^{-6}), and trypsin digestion was used to facilitate the production of monocellular films. 2 hours later cell squashes were prepared using hypotonic citrate and Feulgen staining in the sequence described by Ford and Hamerton (1956). Mitoses were maximal at 72 hours but only a few could be found before 24 hours, and they were very scarce after 124 hours. The reason we employed tissue-culture techniques in this determination was the relative paucity of mitoses in this patient's previous metastases, and the demonstration by Tjio and Puck (1958) of the stability of chromosome number in tissue culture.

Results

We observed about 100 squashed cells in metaphase (" plates ") all being obviously diploid. Because of overlapping of chromosomes, however, most were not photographed. Four plates had good chromosome separation which allowed accurate counting and charting. The chromosomes numbered forty-six in each instance, and, by comparison with published chromosome maps (Ford et al. 1959a and b), they suggest a normal female distribution with the XX allelomorph (fig. 1). Many intact nuclei showed the Barr chromatin body (fig. 2).

For the following reasons we felt that most mitoses represent mitotic activity in tumour tissue rather than in the supporting host tissue:

(1) Microscopically the tumour showed relatively little tissue other than that of teratomatous nature (fig. 3).

(2) Histological observation of the explanted tissue showed abundant epithelial growth at the time of maximum mitotic activity in the squashes, while there was obvious fibroblastic overgrowth after 100 hours with considerable coincident decline in the number of mitoses in the later squashes.

Discussion

The diploid nature of this teratoma is complementary to the almost universal finding of sex chromatin in the nuclei of teratomas arising in females. As was expected the chromosome determination of this tumour does not furnish the answer to the origin of teratomas. Similar studies of teratomas in males will be necessary. The infrequency of these tumours makes such a prospective analysis difficult. Investigators having access to foals, in which benign teratomas of the testis are found relatively frequently at the time of gelding (Willis and Rudduck 1943), will be in a more favourable position to investigate the genetic origin of teratomas.

Summary

Examination of squashed cells in metaphase from a colonic metastasis of an ovarian teratoma showed that the chromosomes numbered forty-six, suggesting a normal female distribution with the XX allelomorph.

We are grateful to Prof. A. T. Hertig for the support of M. G. from the Henrietta Briggs Payson Fund for Cancer Research to Harvard Medical School, and we acknowledge the valuable assistance of Mrs. M. Moore, Mrs. M. La Gattuta, and Mrs. J. W. Richart. This work was supported by research grant RG 4966 from the United States Public Health Service.

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TREATMENT OF CEREBRAL FAT-EMBOLISM

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SEVERE fat-embolism is manifested by a symptom complex that includes evidence of widespread focal damage to lungs, central nervous system, and retinæ associated with cutaneous and conjunctival petechiæ and fat globules in sputum and urine.

Fat-embolism is especially liable to follow fractures of the long bones and soft-tissue injuries (Alldred 1953, Johnson and Svanborg 1956) and it is commoner in the well-nourished than in the lean (Zeithofer and Reiffenstuhl 1952). From experience in the 1939–45 war its importance has been emphasised by Robb-Smith (1941), Wilson and Salisbury (1944), Newman (1948) and Grant and Reeve (1951) in this country; and the reports of these and other workers (Glas et al. 1953, Swank and Dugger 1954, Saikku 1954, Scully 1956) leave little doubt that it is one of the most important causes of mortality and morbidity following trauma. Saikku (1954) found that it accounted for 8 out of 25 deaths in 881 consecutive cases of fractures; his series included 2 cases of fat-embolism in which the patient survived.

The mechanism of fat embolism is undecided.

Fragments of bone-marrow are rarely found post mortem in the lung vessels (Armin and Grant 1951). Fat droplets are probably released into the vascular system at the site of trauma and circulate to the lungs, where the largest amount of fat embolism is found post mortem. Some globules of fat traverse the lung vessels and are found in many organs, where they may give rise to petechial hæmorrhage. The kidneys are most commonly involved according to Scully (1956), who states that the presence of fat in the renal vessels is the most sensitive pathological index of the entrance of fat emboli into the systemic circuit. Many workers believe, however, that fat already present in the blood contributes to fat-embolism. For example, Swank and Dugger (1954) stated that an " important source of the fat emboli is circulating fat globules which are held much of the time in the capillaries of the general and pulmonary circulation. The circulating fat probably has its origin from the chylomicra, and it is increased by heavy feeding for several weeks and decreased by fasting."

Symptoms usually develop within 3–72 hours of the trauma (Warren 1946) and can be attributed largely to widespread embolism in the small vessels of the lungs and brain.

Restlessness, breathlessness, chest pain, cyanosis, and widespread adventitious sounds in the lungs suggest pulmonary involvement, and X-ray findings of focal opacification of the lungs confirm the clinical diagnosis. Cerebral involvement is evidenced usually by irrational behaviour, epileptiform phenomena, paralysis, or coma. Petechiæ in skin, conjunctivæ, or retinæ and fat in the urine (and, less specifically, in the sputum) are useful in diagnosis. Fever is usually present and is sometimes attributed to disturbance of the heat-regulating mechanism in the brain. Symptoms of lung or brain involvement may occur independently of each other or may coexist. There is good evidence, however, that pulmonary fat-embolism

is not very severe clinically, and Armin and Grant (1951) state that " in injured man also pulmonary fat embolism is unlikely to cause obvious symptoms or to be alone or in part responsible for death." It is the widespread focal embolism and hæmorrhage in the brain that constitute almost the whole importance of the clinical syndrome. Alldred (1953) states that the prognosis is grave in those patients who develop sudden deep coma, whereas those with drowsiness or irrational behaviour and relatively minor symptoms of brain damage have a good chance of survival.

Diagnosis of cerebral fat-embolism is difficult, particularly in patients with multiple injuries and especially if there is injury to the head. Confusion with such lesions as extradural hæmorrhage, subdural hæmorrhage, or mid-brain injury is common (Schneider 1952).

There is no standard prophylaxis, although care in immobilising fractures and in the transport of the injured may be of value. Ligature of veins draining fractured sites is of doubtful efficacy (Newman 1948, Saikku 1954).

As regards the established case of severe cerebral fat-embolism, there is only gloom regarding treatment.

According to Denman and Gregg (1948) " Until diagnosis becomes reliable no rational plan of active therapy can be formulated." Aird (1949) shared this gloomy outlook, and avers that " most patients who suffer from fat embolism probably recover but those in whom the diagnosis is made during life usually die ".

Attempts at specific treatment—for example, by the intravenous injection of such agents as sodium carbonate or sodium desoxycholate (Robb-Smith 1941)—have not been very successful. Because of its known effect in clearing lipæmic plasma, heparin was used in the treatment of experimental fat-embolism, but appeared to be of no value or even dangerous (Gardner and Harrison 1957); but Sage and Tudor (1958) treated 3 patients with heparin and all recovered.

The chief danger in fat-embolism is long-continued coma. In the following case the application of modern principles of coma management saved the life of a 16-year-old girl with prolonged coma.

Case-report

A filing clerkess, aged 16, was knocked down by a motorcar on the evening of Nov. 22, 1957, sustaining comminuted fractures of the right tibia and fibula and a laceration of the right eyebrow. She was admitted promptly to hospital and she was then quite rational; she had not lost consciousness at any time and gave a detailed account of the accident. She received morphine gr. $^1/_4$ for relief of pain and an injection of 1 ml. antitetanic serum. Examination showed no abnormality, except at the sites of injury. There was considerable swelling of the soft tissues at the fracture site, and this increased during the hour prior to reduction. Under general anæsthesia the fractures were reduced, Steinman skeletal transfixion pins were inserted through the tibial shaft half-way between the fracture site and the ends of the bone, and a loosely padded plaster cast applied. The laceration over the eyebrow was sutured.

On return to the ward the patient failed to recover consciousness. At first she responded with movement to painful stimuli, and pupillary reactions were normal. There appeared to be much fluctuation in muscle tone in the limbs, and about noon on Nov. 23 an extensor plantar response developed on the left side (the injured leg was not examined). She was incontinent of urine and vomited several times. During the day coma gradually deepened and cerebral fat-embolism was suspected. Her blood-pressure remained about 105/85 mm. Hg. On Nov. 24 she was in deep coma with her head turned constantly to the left and her limbs outstretched. She had increased muscle tone, brisk tendon reflexes, and bilateral extensor plantar responses. Her jaws were tightly clenched and her mouth could not be opened. She was cyanosed, and pulse-rate, temperature, and respiratory rate were increased. Petechiæ were noted in the posterior triangles of the neck and on the front of the chest and abdomen, and inspection of the fundi showed a small hæmorrhage and a patch of œdema at the right macula. Cerebral fat-embolism was diagnosed and the patient was prepared for treatment of protracted coma.

The following steps were taken:

Prevention of pneumonia.—Tracheotomy was performed on Nov. 24, and ' Crystamycin ' was administered from Nov. 24 to Dec. 12.

General nursing care.—The patient was screened off in the general ward and kept under the care of a special nurse. The heavy plaster and the rigidity of limbs made nursing difficult; but frequent turning and skin toilet were carried out satisfactorily, though two small bedsores eventually formed on the left leg. Incontinence was prevented by an indwelling bladder catheter so that the plaster cast could be kept dry (the hazard of urinary infection was recognised). Apart from one short episode of diarrhœa (vide infra) the large bowel gave no trouble.

Fluid balance and feeding.—No fluid had been given during the first 2 days in hospital. On Nov. 25 intravenous therapy was begun. With the exception of one day (Nov. 30) when rectal saline was given, the patient was maintained with intravenous feeding until Dec. 11. Glucose solution was given initially for 5 days and then an electrolyte solution (containing sodium, potassium, magnesium, chloride, bicarbonate, and phosphate) was added. The fluid needs were underestimated initially and the patient had oliguria for some days. The blood-urea was raised initially but soon fell to normal, and this episode of azotæmia was probably due entirely to the inadequate water intake. The urine was highly concentrated, and there was no evidence of tubular insufficiency. The infusions were given without difficulty through lengths of polyethylene tubing into arm veins. On Dec. 8 additional feeding was given by intragastric tube. As soon as this was well established, intravenous feeding was stopped (Dec. 11). Because the patient had moderate anæmia blood-transfusion (2 pints) was given before the intravenous infusion was stopped. Milk was given initially in the gastric drip, but eventually this was fortified with protein hydrolysate, glucose, and vitamins. When too rich a mixture was given, the patient had watery diarrhœa for about three days. Sips of water were first taken on Dec. 15 and small mouthfuls of food on Dec. 21. However, intragastric feeding had to be continued until Dec. 31 (i.e., until the 40th day after the accident) as it took about 2 weeks for the patient to recover fully her ability to eat properly. During the period of intravenous feeding, vitamins C and B complex were given parenterally.

Control of pyrexia.—Pyrexia in fat-embolism is sometimes thought to be due to brain damage. The risk of hyperpyrexia was feared, and because of this the patient was eventually nursed with almost the whole body exposed. This procedure was adopted empirically at the end of the first week and may have accounted for the fall in temperature, pulse-rate and respiratory rate at that time.

Bladder care.—An indwelling catheter was required for some weeks to prevent soiling and frequent changes of plaster cast and also to ensure adequate care of skin. Urinary-tract infection was inevitable, and pyuria and recovery of various organisms (*Escherichia coli*, *Pseudomonas pyocyanea*, staphylococcus, &c.) on culture were recorded during the period of catheterisation. Crystamycin given initially to prevent pneumonia would also have been partially protective against urinary infection, and when it stopped (Dec. 12) treatment was continued with oral sulphonamides.

Course of Illness

Throughout the first week the patient remained in coma, responding only to hard pinching by faint grimacing and slow withdrawal movements. Her head and eyes were turned to her left, the eyes sometimes showing skew deviation. The pupils reacted to light. Her limbs were extended and internally rotated, her jaws and hands closed, and her eyes shut. Fundal œdema began to subside in the second week, and, as if in parallel to the commencing resolution of the cerebral lesions, she responded more readily to painful stimuli, sometimes briefly opening her eyes, when a menace reflex could be elicited. Coincidentally, a slight right facial weakness became apparent. Muscle tone increased notably to rigidity.

By the third week, she began to respond to shaking and calling, opening her eyes, and looking towards the source of stimulation for very brief periods, but it was not until the end of this week that she recognised her relatives. At this time, the intravenous therapy was replaced by intragastric feeding, and her arms became firmly adducted and flexed in the decorticate

posture. Spontaneous grimacing and occasional slow, sneering smiles were observed.

In the fourth week she occasionally raised her head from the pillow, and attempted to grasp objects placed in her hands. She awoke spontaneously for brief periods, and examination provoked grimacing and weeping.

Voluntary swallowing of semi-solids in the fifth week allowed removal of the tracheotomy tube on the 30th day, but oral feeding was not fully established for another week, when the intragastric tube was withdrawn. Concurrently she became a little more cheerful, smiling more frequently. There was gradual lessening of the rigidity, and her arms slowly unflexed, the left less quickly than the right.

In the sixth week, she spoke for the first time. Initially her speech was very dysarthric, scant in quantity and poor in quality, and rarely spontaneous.

By the seventh week, she could read a few words in large headline print, and name stage and screen personalities from their pictures. By this time the only fundal abnormality was alteration in the light reflex in the areas where hæmorrhages had been previously noted. Together with gradual return of voluntary muscular activity, she became more selfconscious and emotionally labile. Formal testing of mental functions was impossible, but a series of simple tests in brief sessions revealed nominal dysphasia, paraphrasia, naming by function, inability to abstract, situational agnosia, and impairment of partial figure recognition. On the 64th day she made her first attempt at writing her name, and thereafter her writing improved slowly but steadily.

In the next 14 weeks there was a slow but steady return in function. Emotionally the patient passed from an irritable and often " weepy " phase to frank euphoria. A real interest in her personal appearance was not displayed until the 20th week. Easy distractibility and poor concentration precluded adequate testing of mental functions, though by the 19th week, with much prompting and repetition of questions, she scored a mental age of 11–12 years in the Kent oral norms emergency test. Her speech became progressively less dysarthric, more spontaneous, and, from a telegram or " pidgin English " type, approached normality in syntax and construction.

With the removal of the plaster cast in the 14th week, she was allowed out of bed. She started partial weight-bearing in the 19th week and was soon walking with the aid of tripod sticks. Her gait was very spastic. All tendon reflexes remained much exaggerated, and the plantar responses were extensor. By the 20th week she was fully continent. She was discharged home on May 6, 1958, 166 days after her admission. She subsequently attended for physiotherapy as an outpatient and continued to make steady progress.

A year after her accident, her mental condition had recovered sufficiently to allow the application of various standard mental tests. Her school record at the age of 12 had indicated average intelligence and attainments (Moray House I.Q. 101; school marks 45–50%). She now scored as " dull normal " (I.Q. 86) on the Wechsler adult intelligence scale (W.A.I.S.), and grade IV (" definitely below average ") on progressive matrices. Her verbal score on the W.A.I.S. and her " average " score on the Mill Hill vocabulary scale suggested some deterioration possibly attributable to organic damage, but the Shipley Hartford deterioration scale yielded no evidence since her vocabulary score was itself too low.

In personality and behaviour her recovery was remarkably complete. Before her accident she was active and cheerful, interested mainly in skating and dancing, and reading little. Neither patient nor persevering, she had been notably quick-tempered and at times wilful and impulsive. A year after embolism both the patient and her mother considered that she showed no radical change in these traits, though some were more pronounced. She had also become more self-conscious, possibly because of her continuing physical handicap. The Minnesota multiphasic personality inventory gave a profile (coded '861*9*374–(69) 8: 9: 17.) which mildly emphasised these tendencies to self-conscious withdrawal, together with a relatively high Mf (" interest ") score whose significance is not clear but which may indicate only her adolescent stirrings.

On Nov. 21, 1958, electroencephalography (E.E.G.) showed abnormalities, especially pronounced in the left temporal region, which were reported by Dr. P. G. Aungle as " compatible with the clinical history of multiple scattered brain lesions."

At this time she still had slight spasticity of the lower limbs, minimal right lower facial weakness and impaired cutaneous sensation along the outer border of her right foot. She could walk more than a mile, use public transport, and go shopping. She had not yet resumed dancing or skating, and she displayed no enthusiasm about returning to work; but otherwise she was more or less her previous self. She is going to be retrained at an industrial rehabilitation centre.

Discussion

This young woman suffered multiple diffuse embolism scattered throughout the brain substance, probably most concentrated in the left temporal area (an E.E.G. indication, perhaps corroborated by the late survival of paraphrasic disturbance). As a result she was reduced to a state of mindlessness in which the central nervous system functioned at a decorticate level. Neurologically, she still has mild spasticity, but psychiatric and psychological examination has revealed no unequivocal evidence of deterioration of intellect or character.

Since brain damage is due to petechial hæmorrhage at the sites of fat-embolism in the small vessels, we would doubt the efficacy of administering heparin at any time except the earliest stage of the illness, and consider its administration even hazardous in that it might promote hæmorrhage. It is likely, however, that in the majority of cases, purpuric hæmorrhage will precede clinical diagnosis and heparin will be contraindicated. In such cases, good nursing and medical management are required until the areas of hæmorrhage in brain and elsewhere resolve. Some of the brain damage may be permanent, but it is remarkable how excellent clinical recovery may be even after such severe coma as in our patient, in whom, indeed, it is by no means certain that recovery is yet final.

Summary

A 16-year-old girl developed typical clinical features of fat-embolism with coma following a fracture of tibia and fibula.

Her condition improved steadily during the year following her accident, and the sequelæ at the end of a year were mild spasticity of limbs and possibly slight intellectual loss. Her recovery, however, was sufficient to enable her to lead a normal life.

This patient was under the care of Mr. I. S. Smillie and Mr. George Sturrock and we are grateful to them and also to Prof. I. G. W. Hill, Dr. A. A. Douglas, and Dr. R. Cowley for advice. We wish to record our appreciation of the skilled nursing of Sister J. B. Elder and her staff. One of us (I. M. S.) is in receipt of a grant from the Scottish Hospital Endowments Research Trust.

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A COMPARISON OF THE DIURETIC ACTION OF THE CHLOROTHIAZIDE ANALOGUES

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SINCE the introduction of chlorothiazide as an orally effective diuretic, two closely similar substances, hydrochlorothiazide and hydroflumethiazide, have been found to be effective diuretics (Blagg 1959, Edmonds and Wilson 1959, Fleming et al. 1959, Kennedy et al. 1959). The most notable difference between the two newer derivatives and chlorothiazide is in the dose required to produce diuresis. Most observers agree that 100 mg. of hydrochlorothiazide or hydroflumethiazide causes a diuresis of a magnitude similar to that caused by 1 g. of chlorothiazide. Edmonds and Wilson (1959) have compared the effect of the three diuretics in two normal subjects and have found that hydrochlorothiazide and hydroflumethiazide have similar effects on renal secretion, in that in equal doses they cause an equal diuresis and similar qualitative changes in the composition of the urine. On the other hand, when hydrochlorothiazide and hydroflumethiazide were compared with chlorothiazide, it was found that the latter substance had a more intense but shorter action in increasing the urinary secretion of water, chloride, and sodium; but, because of the prolonged action of hydrochlorothiazide and hydroflumethiazide, the total excretion of sodium and chloride might be substantially greater than that caused by chlorothiazide. Potassium excretion was increased by all three drugs but was greatest after chlorothiazide. Treatment with hydrochlorothiazide and hydroflumethiazide may, however, lead to hypokalæmia in occasional patients suffering from œdema (Blagg 1959, Edmonds and Wilson 1959). Chlorothiazide inhibits carbonic anhydrase and this causes a transient increase in bicarbonate excretion with consequent changes in urinary pH and titratable acidity (Matheson and Morgan 1958). This effect is less marked after hydrochlorothiazide and hydroflumethiazide.

In the present investigation an attempt has been made to explain the differences in the action of chlorothiazide and its two derivatives by estimating the quantity of each drug which appeared in the urine after oral and intravenous administration; at the same time the effect of the diuretics in altering the quantity and composition of the urine was observed.

Methods

Experimental

Ten healthy male medical students without evidence of renal disease were investigated.

On each day of experiment the person under observation was allowed a fixed and known fluid intake; food intake was roughly similar; normal physical activity was allowed short of strenuous physical exercise. The urine of each subject was collected over a period of 24 hours on four separate occasions. In the first control period no drug was given and in the subsequent three periods the effects of 2000 mg. chlorothiazide, 150 mg. hydrochlorothiazide, and 150 mg. hydroflumethiazide were compared. At least 7 days elapsed for each subject between successive experiments to allow the restoration of normal body-fluid composition. The bladder was emptied at 7 A.M. and at 9 A.M., one or other drug was given by mouth and at that time the urine was collected under mineral oil and thereafter at 2-hour intervals for 12 hours. During the remaining 12-hour period the urine was collected in bulk under oil.

Chemical

Sodium and potassium: by direct flame photometry.

Chloride: by modified Volhard-Harvey titration (Peters and Van Slyke 1932).

Carbon dioxide: by the manometric method of Peters and Van Slyke (1932).

Bicarbonate was calculated from the carbonic acid-bicarbonate curve according to pH (Peters and Van Slyke 1932).

Urine pH: by the glass electrode.

Titratable acidity to pH 7·4: by the glass electrode.

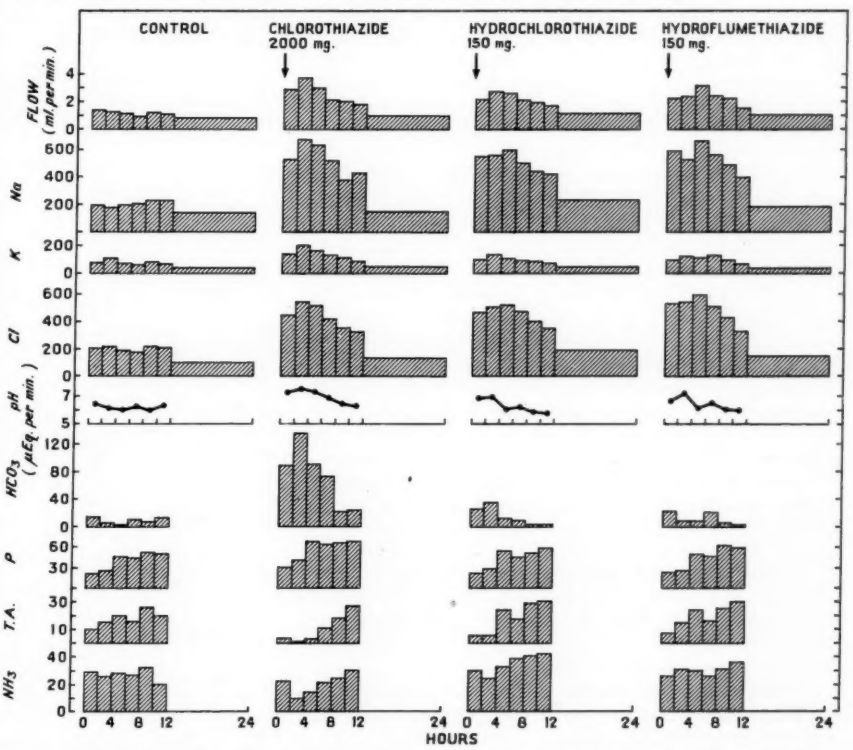

Fig. 1—Comparison of the rates of excretion of electrolyte and urine during 24 hours after oral administration of 2000 mg. chlorothiazide, 150 mg. hydrochlorothiazide, and 150 mg. hydroflumethiazide (averages of ten men).

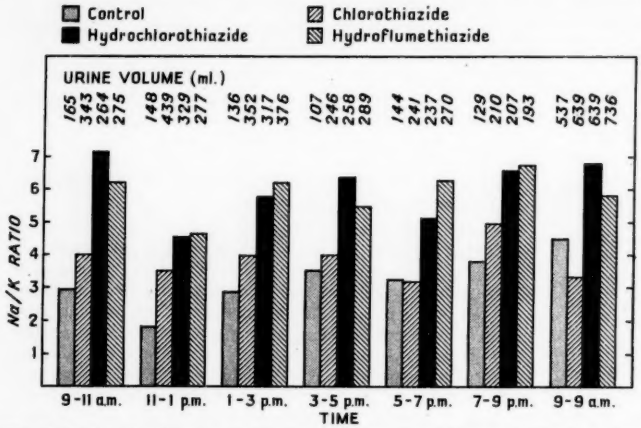

Fig. 2—Ratio of sodium to potassium excretion over 24 hours (average of ten men). The greater sodium to potassium ratio after hydrochlorothiazide and hydroflumethiazide is almost entirely due to a smaller excretion of potassium.

Ammonia: by aeration titration.

Inorganic phosphate: by the method of Fiske and SubbaRow (1925).

Chlorothiazide, hydrochlorothiazide, and hydroflumethiazide were estimated by a colorimetric method modified for each substance from the method of Bratton and Marshall (1939) for sulphonamide estimation.

Results

In fig. 1 the effects of the three diuretics on the rate of urine formation and its composition are compared. The findings agree broadly with those reported by Edmonds and Wilson (1959). It will be seen that the diuretic effect and the pattern of electrolyte excretion after the oral administration of 2000 mg. chlorothiazide, 150 mg. hydrochlorothiazide, and 150 mg. hydroflumethiazide are similar (fig. 1). Under the conditions of these experiments the response to all three drugs appeared within 2 hours of administration, reached a maximum by 4 hours, and in the case of chlorothiazide had largely ceased 12 hours after administration. In the case of hydrochlorothiazide and hydroflumethiazide, sodium and chloride continued to be excreted in quantities in excess of the control for a period up to 24 hours after the drugs were given. Both drugs caused a brief increase in bicarbonate excretion and consequently had less effect on the pH and titratable acidity of the urine than chlorothiazide. Excretion of potassium after hydrochlorothiazide and hydroflumethiazide is rather less than after chlorothiazide. Fig. 2 shows the average ratio of sodium loss to potassium loss during the 24-hour period after each of the three diuretics. While the sodium/potassium ratio is similar during the action of hydrochlorothiazide and hydroflumethiazide, it is considerably lower after chlorothiazide although sodium loss induced by the three drugs is substantially similar during the first 12 hours. Therefore, in a normal subject hydrochlorothiazide and hydroflumethiazide have a longer diuretic effect than chlorothiazide, with less tendency to cause potassium loss and to raise the urinary pH.

These findings are of some clinical significance; but, having regard to the variability of absorption of drugs from the intestinal tract, the action of chlorothiazide and hydrochlorothiazide given in equal dosage by intravenous injection was compared in normal subjects. It was not found feasible to give hydroflumethiazide by intravenous injection, because of the large amount of alkali required to bring this substance into solution. The result of this experiment (fig. 3) broadly confirms the findings observed when the drugs are given by mouth except that the rate of excretion of water and other urinary constituents, particularly potassium, after intravenous hydrochlorothiazide is rather less than after chlorothiazide. In this experiment, since the drug was given by intravenous injection, the dose of hydrochlorothiazide was possibly rather large, and it has been noted by Meyer et al. (1959) that in the dog increasing dosage of hydrochlorothiazide tends to be followed by diminishing diuretic effect. He has suggested that this may indicate some degree of toxic action on the renal tubules.

Excretion in the Urine

Throughout the foregoing experiments the amount of each diuretic in each sample of urine was estimated. The analytical methods employed (to be published elsewhere) consisted essentially in diazotisation and coupling with N(1-naphthyl)ethylenediamine hydrochloride after alkaline hydrolysis in the case of chlorothiazide and acid hydrolysis in the case of hydrochlorothiazide and hydroflumethiazide. From the recovery experiments it was found possible to recover 97–104% of added chlorothiazide, hydrochlorothiazide, and hydroflumethiazide. The methods were not, however, sufficiently sensitive to enable plasma or serum concentrations of the drugs to be determined with a useful degree of accuracy over sufficiently long periods.

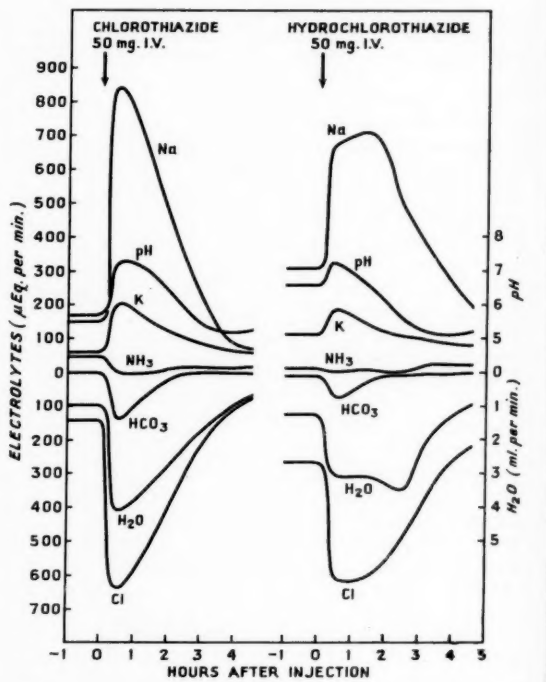

Fig. 3—Comparison of the effect of 50 mg. chlorothiazide and 50 mg. hydrochlorothiazide, by intravenous injection, on water and electrolyte excretion.

Recovery from Urine after Intravenous Administration

Chlorothiazide appeared in the urine in maximum concentration during the first half-hour after the intravenous injection of 50 mg.; thereafter the concentration declined steadily but calculation of the cumulative excretion showed that by $4^1/_2$ hours 100% of the administered drug had been excreted. In the case of hydrochlorothiazide the maximum urinary concentration was seen during the first half-hour but the drug continued to be excreted in measurable quantities for $4^1/_2$ hours and in detectable quantities for 8–10 hours. The total recovery at the end of $4^1/_2$ hours was 54% of the dose. Thus chlorothiazide is more rapidly eliminated than hydrochlorothiazide, since by the end of $4^1/_2$ hours all the drug had appeared in the urine. On the other hand, hydrochlorothiazide continued to be visually detectable in the urine for at least 8 hours after administration, and a trace is likely to be present for much longer. This would be in keeping with the finding previously noted that increased sodium and chloride excretion continues for 24 hours after the oral administration of hydrochlorothiazide.

Recovery from Urine after Oral Administration

When chlorothiazide, hydrochlorothiazide, and hydroflumethiazide were given by mouth in doses of 2000, 150, and 150 mg. respectively, the maximum urinary concentration of all three drugs was found in the urine

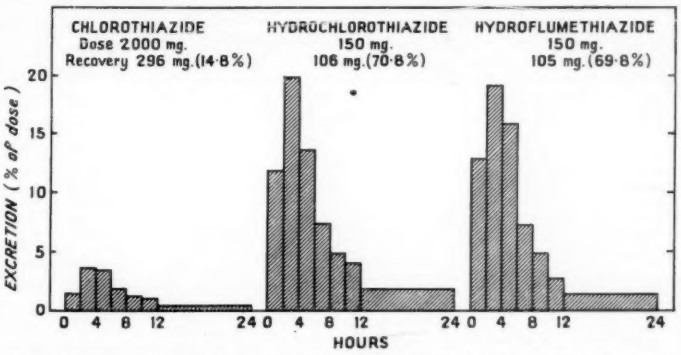

Fig. 5—Urinary excretion of chlorothiazide, hydrochlorothiazide, and hydroflumethiazide during 24 hours following a single oral dose (average of ten men).

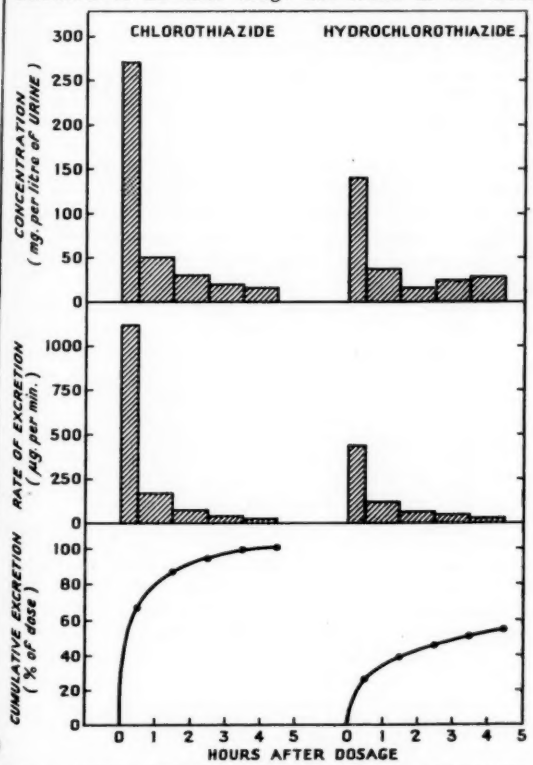
CHLOROTHIAZIDE
HYDROCHLOROTHIAZIDE
CONCENTRATION (mg. per litre of URINE)
RATE OF EXCRETION (µg. per min.)
CUMULATIVE EXCRETION (% of dose)
HOURS AFTER DOSAGE

Fig. 4—Urinary excretion of chlorothiazide and hydrochlorothiazide following a single intravenous dose of 50 mg.

secreted during the first 2–4 hours after administration. Thereafter the concentration declined until by the end of 24 hours it could no longer be detected in the urine. The urine collected during the second period of 12 hours after chlorothiazide contained only a small quantity of the drug while during the same period considerably more hydrochlorothiazide and hydroflumethiazide were recovered (fig. 4). The urine concentration of all three diuretics ran parallel to the diuretic effect. The greatest change in the quantity and composition of urine occurred when the concentration of diuretic in the urine was greatest. When the total recovery of the three compounds was calculated, it was found that over 24 hours the average total recovery of chlorothiazide was 14·8% of the dose administered, with a range of 7·8–28·7%. In the case of hydrochlorothiazide the average total recovery over 24 hours was 70·8% with a range of 61·1–83·4% of the dose ingested, and in the case of hydroflumethiazide the average recovery was 69·8% with a range of 42·1–84·9%. This suggests that the reason why chlorothiazide must be given in a much larger dose than either of the other compounds, to achieve a similar diuretic effect, is that it is incompletely absorbed from the intestine and rapidly excreted as compared with the newer derivatives, or that it is changed chemically in the body to a form which is not detected by the methods of analysis here employed; since, however, 100% of an intravenous dose can be recovered from the urine, the former explanation is more likely.

Summary

The diuretic actions of chlorothiazide, hydrochlorothiazide, and hydroflumethiazide have been compared in ten healthy men.

All three drugs cause diuresis with similar changes in the composition of the urine except that hydrochlorothiazide and hydroflumethiazide are effective in a smaller dose and cause less potassium loss and bicarbonate loss than chlorothiazide.

The action of hydrochlorothiazide and hydroflumethiazide is more prolonged than that of chlorothiazide, particularly as regards the excretion of sodium and chloride.

The prolonged action and the smaller effective dose of hydrochlorothiazide and hydroflumethiazide can be explained by the finding that chlorothiazide is less completely absorbed from the intestine and more rapidly eliminated in the urine than both hydrochlorothiazide and hydroflumethiazide.

We wish to record our appreciation of the cooperation and help given by all the volunteers who took part in the experiment and to thank Dr. J. J. F. Merry of Merck, Sharp & Dohme, Ltd., for generous supplies of chlorothiazide (' Saluric ') and hydrochlorothiazide (' Hydrosaluric ') and also Dr. P. T. Main of Boots Pure Drug Co. for supplies of hydroflumethiazide (' Hydrenox ').

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ACUTE ANOXIC CARDIAC FAILURE IN PULMONARY HEART-DISEASE

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FROM 10 to 25% of patients admitted to hospitals in Britain with congestive cardiac failure have chronic lung disease as the underlying cause (Flint 1954, Wood 1956). Despite this, the problem of pulmonary heart-disease remains relatively neglected when compared with the recent advances in hypertensive, valvular, and atherosclerotic heart-disease.

Lack of a generally accepted classification of pulmonary heart-disease may have played a part in retarding progress in this disorder but it is unlikely that any attempt to change a long-established term such as " cor pulmonale " would meet with general recognition. Pulmonary heart-disease could be more precisely classified as:

(1) Acute pulmonary heart-disease due to massive pulmonary embolus (acute cor pulmonale).
(2) Pulmonary heart-disease due to chronic lung disease.
(*a*) Without cardiac failure.
(*b*) With chronic cardiac failure.
(*c*) With acute cardiac failure.
(3) Pulmonary heart-disease due to pulmonary vascular disease.

This paper is concerned with the problem of acute anoxic cardiac failure in pulmonary heart-disease and describes the extent of the problem in Edinburgh and the results of treatment, with a suggested scheme of management.

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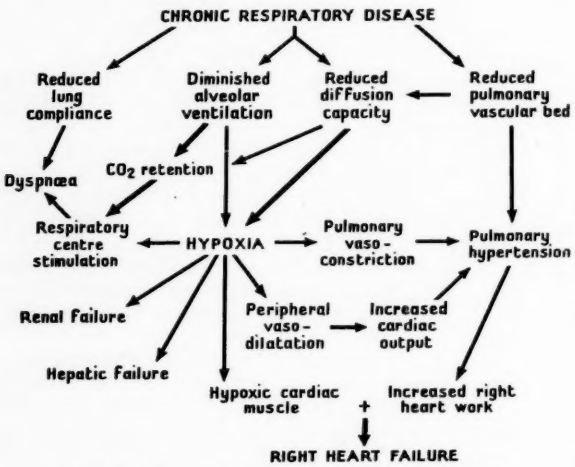

Fig. 1—Importance of anoxia in pulmonary heart-disease.

Physiology and Principles of Treatment

Chronic respiratory disease leads to four main changes which influence blood-gas exchange in the lungs (fig. 1).

Reduction in diffusing capacity tends to lead to hypoxia rather than carbon-dioxide retention because of the more rapid diffusion of carbon dioxide across the thickened fibrotic alveolar wall (Arnott 1957).

Reduction in alveolar ventilation (e.g., in emphysema), however, results in a raised alveolar carbon-dioxide concentration with subsequent elevation of blood-levels to maintain a normal blood-to-gas excretory gradient.

Since diffusion capacity and alveolar ventilation are generally both affected in chronic lung-disease, hypoxia and carbon-dioxide retention tend to occur together and when present act as respiratory-centre stimulants. Normally a high carbon-dioxide level has the more potent action but after prolonged elevation the respiratory centre becomes insensitive to carbon dioxide (Motley 1950). Further elevation of blood-carbon-dioxide leads only to intoxication with ultimate coma. Relief of anoxia under these conditions deprives the respiratory centre of physiological stimulation, and the resulting apnœa may lead to carbon-dioxide narcosis. This risk in oxygen therapy is now well recognised (Motley et al. 1947, Comroe et al. 1950, Westlake et al. 1955).

Reduction in the pulmonary vascular bed (Harvey et al. 1951, Bates et al. 1956) and *impairment of lung compliance* (Cherniack 1956) also affect blood-gas exchange in the lungs, although they may have an even greater influence on pressures in the pulmonary circulation. Some degree of pulmonary hypertension is a frequent accompaniment of chronic lung disease (Dexter et al. 1950), especially in the presence of cardiac failure (Mounsey et al. 1952). Moreover pulmonary hypertension is probably not solely the result of mechanical reduction in the vascular bed since it is known that hypoxia itself produces active pulmonary vasoconstriction (Motley et al. 1947, Doyle et al. 1952).

Effect of Acute Respiratory Infection

A balance is ultimately attained when reasonable function is preserved despite relative anoxia and carbon-dioxide retention (Wilson et al. 1951). An acute respiratory infection under these conditions by causing additional obstruction to gaseous exchange may be sufficient to upset the balance and precipitate acute anoxia (Kritzler 1944). Under these conditions Platts (1953) found that the arterial oxygen saturation frequently fell below 72%. The sharp fall in oxygen saturation below the previous hypoxic levels often found in chronic lung disease affects all tissues.

Peripherally there is marked vasodilatation (McMichael and Sharpey-Schafer 1944). Centrally, despite the increase in cardiac output (Fishman et al. 1952), anoxia results in pulmonary vasoconstriction. The result is an increase in pulmonary-artery pressure with increased strain on the right side of the heart. This in itself may be insufficient to cause right-ventricular decompensation were it not for the anoxia of cardiac musculature which plays a part in the ensuing cardiac failure. The hypoxia is generalised and other organs are also affected. Both renal and hepatic failure may occur as added complications (Simpson 1957), while neurological disturbances are well recognised (*Lancet* 1957).

Relief of Anoxia

Relief of anoxia is fundamental in the treatment of acute anoxic cardiac failure complicating pulmonary heart-disease, and, as stated above, the problem is to maintain sufficient frequency and depth of respira-

tion to avoid carbon-dioxide narcosis whilst administering oxygen continuously. In the past there has been a tendency to be content with inadequate oxygenation.

Intermittent use of oxygen leaves patients deeply anoxic for about half of each hour. Satisfactory arterial oxygen saturation is seldom possible by such measures and the danger of carbon-dioxide intoxication still persists (Westlake et al. 1955).

Slow continuous administration of oxygen maintains the oxygen saturation below 85% but preserves some "anoxic drive" to the respiratory centre (Simpson 1957, Westlake and Campbell 1958). This method of treatment is suitable in the less severely affected patients but in those who are comatose or semicomatose it is less feasible. It is in effect a compromise between continuous oxygen therapy and the fear of carbon-dioxide narcosis. It fails to offer the benefits of maximally attainable oxygen levels, whilst requiring careful detailed management.

The use of a mechanical respirator appears to provide the most satisfactory method of avoiding carbon-dioxide narcosis whilst giving continuous oxygen therapy (Stone et al. 1953, Lovejoy et al. 1954, Austen et al. 1957). Unfortunately the average general hospital has neither the staff nor the facilities available to provide this expensive, time-consuming, and specialised treatment. At present, therefore, there is no readily available and generally accepted method of giving continuous oxygen therapy in acute anoxic cardiac failure.

Clinical Features

Clinically pulmonary heart-disease and anoxic cardiac failure are characterised by cyanosis, dyspnœa, peripheral vasodilatation, and signs of right-sided cardiac failure. Often in addition there is evidence of carbon-dioxide narcosis with drowsiness, confusion, muscular twitching, and occasionally even coma. When precipitation of cardiac failure has been rapid, œdema is frequently minimal despite considerable elevation of the jugular venous pressure and considerable liver enlargement. Under these conditions the respiratory infection may so dominate the clinical picture that cardiac failure is readily overlooked. Less frequently there are signs of peripheral circulatory collapse with marked œdema, cold extremities, and absence of peripheral vasodilatation (Wood 1956). Patients showing these features are usually severely ill, and the diagnosis may be passed over in favour of intramural myocardial infarction since the electrocardiographic (E.C.G.) changes are not dissimilar.

As the respiratory infection subsides cardiac failure usually settles gradually. If patients can be tided over the acute period reasonable recovery often takes place. Once cardiac failure regresses objective proof of pulmonary heart-disease is frequently difficult since E.C.G. and chest radiography frequently fail to confirm the presence of right-sided cardiac involvement (Armen et al. 1958).

The Present Series

To assess the extent of the problem in Edinburgh three hundred and thirty-four consecutive patients admitted with congestive cardiac failure were reviewed. In 25% there was a history of chronic lung-disease and in 15% this was the sole ætiological factor in the cardiac failure (table I). Men predominated in the ratio of 3 : 1. Of the 15% with pulmonary heart-disease uncomplicated by other cardiac disease there were forty-four patients with acute cardiac failure. These were further studied to determine which factors influenced the resultant prognosis.

The mortality was 41% (table IIA), without significant difference between sexes. All patients had been treated

TABLE I—ÆTIOLOGICAL FACTORS IN 334 CONSECUTIVE PATIENTS WITH CONGESTIVE CARDIAC FAILURE

Disease	No. of patients
Valvular and congenital heart-disease	81 (24%)
Hypertensive heart-disease	42 (13%)
Coronary artery disease	77 (23%)
Chronic lung disease	50 (15%)
Mixture of two or more of above	78 (23%)
Miscellaneous	6 (2%)

with antibiotics. Although a number received treatment with digitalis or diuretics there was no significant difference in prognosis between those receiving digitalis, diuretics, digitalis and diuretics, or neither of these drugs. Of all factors studied only the E.C.G. findings bore a relationship to the prognosis.

Of the nineteen patients with right-ventricular strain (Goldberger 1954) fourteen died, eight of these within 4 days of admission (table IIB). By comparison, only four of the patients who did not show this E.C.G. pattern failed to survive admission to hospital. Minimal evidence for right-ventricular strain was considered to be present when asymmetrical T-wave inversions appeared in V_3R, V_4R, V_1 and V_2. Usually the T-wave inversions extend across the chest leads as far as V_4 or V_5.

From these observations it seemed possible to define a separate group of patients with pulmonary heart-disease for whom the prognosis in an acute exacerbation was particularly poor. As these patients had been treated with neither respiratory stimulants nor continuous oxygen they formed a sufficiently well-defined group to compare with others treated by the suggested scheme of management.

Selection of Patients

The patients selected for trial of therapy were all those admitted because of acute cardiac failure with pulmonary heart-disease as the sole ætiological factor and right-ventricular strain in the E.C.G. Before treatment chest X-ray, blood-electrolyte, arterial oxygen and carbon dioxide, and E.C.G. investigations were performed, and sputum was collected for culture.

Method of Treatment

The principle of treatment was to provide continuous oxygen therapy avoiding carbon-dioxide narcosis by the frequent use of respiratory stimulants, while antibiotics were given to help overcome the respiratory infection.

For at least 3 days patients were maintained in an oxygen tent. In addition to continuous oxygen they had regular injections of respiratory stimulants.

The frequency of administration and the necessity for additional intravenous doses was governed by the clinical condition. Where there was evidence of carbon-dioxide

TABLE IIA—OUTCOME IN 44 CONSECUTIVE PATIENTS WITH ACUTE ANOXIC CARDIAC FAILURE DUE TO LUNG DISEASE

—	No. of patients	Died	Survived	Mortality (%)
Males	32	13	19	40
Females	12	5	7	42
Total	44	18	26	41

TABLE IIB—MORTALITY AND THE PRESENCE OR ABSENCE OF RIGHT VENTRICULAR STRAIN

—	No. of patients	Died	Survived	Mortality (%)
E.C.G. showing strain	19	14	5	74
E.C.G. showing no strain	25	4	21	16

narcosis before treatment began, 5 ml. of nikethamide was given intramuscularly 2-hourly. Such patients in addition received 30 mg. of amiphenazole (' Daptazole ') intramuscularly 2-hourly as a further respiratory stimulant. The injections of nikethamide and amiphenazole were alternated so that patients were receiving a stimulant every hour. When, despite this, signs of narcosis became more apparent after commencing oxygen therapy, additional doses of nikethamide were administered intravenously in doses of 4 ml. at intervals of not less than half an hour. Where there was no evidence clinically of carbon-dioxide narcosis before treatment nikethamide alone was given, 5 ml. 4-hourly. Signs of narcosis were considered an indication for more frequent doses of respiratory stimulants.

After 72 hours initial attempts were made to reduce the frequency of respiratory stimulants. Where decreasing frequency of nikethamide did not result in respiratory depression stimulants were discontinued by stages. Once respiratory infection was abating and clinical improvement was apparent, oxygen therapy was discontinued by degrees. The rapidity of this procedure depended upon the tendency for reappearance of cyanosis, and there was

TABLE III—CARBON-DIOXIDE COMBINING POWER AND NEUROLOGICAL SIGNS

Case no.	Neurological changes	CO_2-combining power (mEq. per litre) a	b	c	Alive or dead	Day of death
1	+ +	34·8	37·0	32·5	A	..
2	+ + + +	33·9	36·4	29·0	A	..
3	+ + +	33·9	44·3	34·5	A	..
4	+ + +	30·4	34·8	31·8	D	10
5	−	36·6	44·3	30·8	A	..
6	+ +	34·3	38·8	24·2	A	..
7	−	25·1	34·8	41·2	D	22
8	+ +	29·9	37·0	37·0	D	18
9	+	39·8	44·8	32·5	A	..
10	+	34·3	36·6	31·2	A	..
11	+	33·6	38·9	29·7	D	33
12	+	36·3	40·8	36·6	A	..
13	−	36·2	38·8	38·8	D	5
14	+ + +	35·7	43·9	33·0	A	..
15	+	32·5	33·6	26·0	A	..
16	+	34·8	37·5	32·5	A	..
17	+ +	32·1	34·2	29·5	A	..
18	+ +	32·1	36·3	29·2	A	..

\+ mild narcosis
\+ + moderate narcosis
\+ + + semicoma
\+ + + + coma

a = on admission
b = maximum elevation
c = prior to death or discharge

no limit to the number of days necessary for this to be completed.

Antibiotics were given before the results of sputum culture became available.

Where the sputum had been mucopurulent for longer than 6 months the antibiotic chosen was chloramphenicol and was given by mouth, 500 mg. 6-hourly for 7 days. When the sputum became reinfected within a few days of completing this course, tetracycline, 500 mg. 6-hourly, was administered by mouth for a long period. Where the sputum had become mucopurulent within 6 months the initial antibiotic used was penicillin, 500,000 units intramuscularly 6-hourly. When sputum culture revealed that the organism was insensitive to the antibiotic used, or the sputum remained infected and the temperature elevated after 4 days of treatment, another antibiotic was substituted.

To simplify interpretation of results, neither digitalis nor diuretics were given during the initial 4 days in hospital. Antispasmodics were given when indicated. Sedation was necessary in all patients and pethidine was used in doses of 50–150 mg. In those with clinical evidence of moderately severe carbon-dioxide narcosis levallorphan was also given to counteract possible depression of the respiratory centre. The dosage used was 2 mg. per 100 mg. of pethidine.

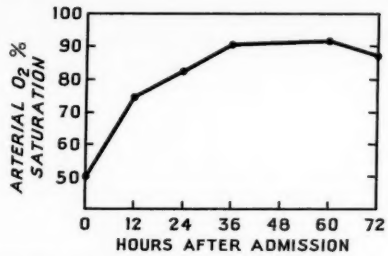

Fig. 2—Arterial oxygen saturation during the first 72 hours of treatment in case 17.

Results of Treatment

Eighteen patients, with an average age of 60, were treated with continuous oxygen therapy and respiratory stimulants. In no instance was the development of carbon-dioxide narcosis such that oxygen therapy had to be discontinued.

All but two patients showed some evidence of carbon-dioxide narcosis on admission (table III). During the initial 2-7 days of treatment carbon-dioxide combining power rose further from a range of 25·1–39·8 to 33·6–44·8 mEq. per litre. Drowsiness tended to increase during the first 48 hours and eight patients required supplementary intravenous injections of nikethamide to prevent coma developing. Where patients were very drowsy before meals a supplementary intravenous injection 10 minutes before eating usually ensured that they could feed themselves. After 3–14 days blood carbon-dioxide levels began to fall so that finally when discharged from hospital six patients had values within normal limits. There was no close correlation between carbon-dioxide combining power and the degree of narcosis, either on admission or subsequently.

The average time for which respiratory stimulants were given was 5·6 days, the range being from 3 to 12 days. Continuous oxygen treatment was continued for an average of 9·4 days (the extremes of treatment being 4–15) before discontinuing by stages. Two men, both with vital capacities of less than 1500 ml., continued to require oxygen intermittently throughout their stay in hospital and later at home. In ten patients arterial oxygen-saturation estimations were performed. These varied on admission from 48 to 76%, the average being 66%. In a few patients levels of 85–90% were present within 12 hours of commencing treatment but in most, despite continuous oxygen administration, it was more than 24 hours before arterial oxygen saturation of 90% was recorded consistently (fig. 2). The estimations prior to discharge varied from 82 to 94% saturation.

Five of the eighteen patients died. Compared with the other group there was a reduction in mortality-rate in those treated with continuous oxygen therapy from 74 to 28% (table IV). This improvement was particularly apparent for the initial 4 days in hospital when there were no deaths in the group treated by the suggested scheme of management and 8 deaths in the other group. After the first 96 hours the mortality-rates showed no significant difference. Of the five

TABLE IV—MORTALITY-RATES IN THE TWO GROUPS OF PATIENTS

	Patients treated with continuous oxygen and respiratory stimulants	Patients treated without continuous oxygen or respiratory stimulants
Survived admission ..	13	5
Died	5	14
% mortality	28	74
Days in hospital before death:		
1	0	2
2	0	4
3–4	0	2
5–10	2	1
11–20	1	2
21+	2	3

patients treated with continuous oxygen therapy who died, only one did so as the direct result of pulmonary heart-disease and cardiac failure (case 8).

Of the others case 13 was admitted and died in status asthmaticus. At necropsy many of the smaller bronchi and bronchioles were obstructed by plugs of viscid secretions, and death was due principally to respiratory obstruction. Another (case 11) who had developed a deep venous thrombus in the leg was about to be discharged when he collapsed suddenly in the ward and died. At necropsy a recent large twisted thrombus $4^1/_2$ in. long was found in the right main pulmonary artery.

Another man (case 4) was given omnopon on one occasion instead of pethidine. The following morning he was found apnœic and deeply comatose with signs of peripheral circulatory failure. Despite an initially satisfactory response to levallorphan he developed anuria which failed to respond to treatment by the Bull regime (Bull et al. 1955). Necropsy showed acute tubular necrosis in the preregenerative phase, and there were changes in the central nervous system resulting probably from anoxia.

The fifth patient who died (case 7) had appeared to respond satisfactorily to treatment, but on the 21st day he became restless and dyspnœic, with a pulse-rate of 140. There was no increase in the amount of sputum or rise in temperature to suggest a further respiratory infection. He died the next day in extreme peripheral circulatory failure. Necropsy showed extensive hæmorrhages in both adrenals, while histologically the glands were virtually obliterated by diffuse hæmorrhages and infarction.

Progress in Hospital

Satisfactory oxygenation and clinical improvement was evident in most instances within 3 days of commencing treatment and usually respiratory stimulants were unnecessary after the 5th day. Despite this, however, œdema tended to increase during this period and the average time taken for its disappearance was 15 days (table V). When discharged from hospital all thirteen patients were free from cardiac failure.

The results of sputum culture became known on the 2nd or 3rd day of treatment. On six occasions no pathogens were isolated. In the remaining patients pneumococci were cultured on five occasions, *Hæmophilus influenzæ* on four, staphylococci on two, and hæmolytic streptococci on one which were considered to be possibly pathogenic.

Before commencing therapy eight patients showed right-ventricular hypertrophy in addition to right-ventricular strain electrocardiographically, while ten showed right-ventricular strain alone. After treatment eight patients showed no change in the E.C.G.; two showed a change from right-ventricular hypertrophy and strain to right-ventricular hypertrophy alone; one showed change from right-ventricular hypertrophy and strain to a normal E.C.G.; and one showed change from right-ventricular strain to hypertrophy and strain. Case 11, who died on the 33rd day, showed change from right-ventricular strain to a normal E.C.G. with treatment. At necropsy the right ventricle measured 10 mm. in thickness. In the remaining four who died the right-ventricular wall was more than 8 mm. thick in each instance. Three of these showed right-ventricular hypertrophy and strain electrocardiographically while one showed strain pattern alone.

TABLE V—COURSE AND TREATMENT OF ŒDEMA

Case	Day of maximal œdema	Day digitalis commenced	Day diuretic commenced	First day of marked diuresis	First day œdema free	Days in oxygen tent
1	6	5	..	9	22	14
2	4	6	14 (M)	10	19	14
3	5	..	5 (M)	5	12	4
5	6	..	..	7	12	8
6	4	..	..	5	12	8
9	5	5	5 (M)	5	15	10
10	10	..	12 (M)	12	18	10
12	4	..	..	6	10	6
14	3	..	..	5	12	6
15	10	9	6 (C) 19 (A)	15	23	14
16	5	5	5 (C)	5	13	8
17	6	..	5 (C)	8	15	10
18	6	5	5 (M)	7	14	8
Average	5·7	..	..	7·6	15·1	..

M = mersalyl. C = chlorthiazide. A = acetazolamide.

Papillœdema was encountered in three patients. This did not increase during oxygen therapy and in each instance the retinæ reverted to normal within 2 weeks. There was no apparent residual damage.

Pethidine proved to be a satisfactory sedative in most instances without causing more than slight respiratory depression. On a few occasions, however, it was not adequate for restless patients, but paraldehyde intramuscularly in doses of 8 ml. was satisfactory. With this sedation no patients proved unmanageable in oxygen tents.

Discussion

Pulmonary heart-disease is as often the cause of cardiac failure as hypertensive heart-disease, and two-thirds as common as atherosclerotic or valvular heart-disease in causing cardiac decompensation. Despite this, since the introduction of antibiotics over 15 years ago, there has been only limited improvement in the management of acute anoxic cardiac failure. Several factors seem responsible for this:

Underestimation of true incidence.—Because it occupies an intermediate position between the specialties of respiratory and cardiac disease there has been a tendency for pulmonary heart-disease to be neglected. Furthermore unless the ætiology of cardiac failure be sought diligently, the diagnosis of this condition may be readily overlooked since in anoxic failure signs of œdema may be minimal initially whilst signs of respiratory infection dominate the clinical picture. In addition E.C.G. and X-ray evidence of right-ventricular hypertrophy are frequently absent (Armen et al. 1958), so that reliance upon ancillary investigations for confirmation of the diagnosis leads to underestimation of the incidence.

Carbon-dioxide narcosis.—It was considered at one time that carbon dioxide may be used to promote respiratory stimulation in anoxic pulmonary heart-disease (Davies and MacKinnon 1949). Appreciation of the relevant physiology however has led to more general awareness of the dangers of carbon-dioxide narcosis in the presence of respiratory-centre insensitivity to carbon dioxide.

That this is not yet as widely recognised as it should be is evident from a recent suggestion (*British Medical Journal* 1958) that 5% carbon dioxide be administered in the treatment of this condition. It is perhaps a reflection of the general lack of interest that Westlake and Campbell alone (1958) were provoked to reply indicating the possibly lethal affects of such an action.

Inadequate treatment of anoxia.—There is even less uniformity of opinion concerning the value of oxygen in acute anoxic cardiac failure. Although the importance of the change from chronic mild anoxia to acute severe anoxia following a respiratory infection is now well appreciated (Bourtourline-Young and Whittenburger 1951, Stone et al. 1953, Westlake et al. 1955, Simpson 1957) the fear of provoking carbon-dioxide narcosis has in the past led to disparagement of continuous oxygen therapy (Flint 1954). Platts (1953) showed that there was a fall in oxygen saturation of 10–20% in patients with acute cardiac failure in pulmonary heart-disease. My findings suggest that this is a conservative estimate in the more severely affected patients who may have a fall in oxygen saturation of 15–35%; this in addition to the chronic degree of anoxia already present in most patients with pulmonary heart-disease. That this degree of anoxia is dangerous is evidenced by reports of hepatic failure (Simpson 1957); renal failure and even anuria (Black and Stanbury 1958); adrenal apoplexy (MacLean and Ironside 1958); and cerebral œdema, hæmorrhage, and atrophy (Courville 1953, Austen et al. 1957). Further examples

of anuria, adrenal apoplexy, and cerebral œdema and atrophy as complications of severe anoxia occur in this series. Moreover it appears likely that the cardiac failure itself is largely a result of cardiac muscle anoxia. Rather than submit to the fear of carbon-dioxide narcosis by failing to relieve anoxia, study of the basic physiology leaves no doubt that oxygen should be administered.

It was an important finding therefore that even severe cases of carbon-dioxide narcosis on admission proved amenable to continuous oxygen therapy when accompanied by the frequent administration of respiratory stimulants.

Although comatose and semicomatose subjects required more frequent stimulation, eight of them with supplementary intravenous injections, the depth and rate of respiration were satisfactorily maintained in all cases and there were no deaths from carbon-dioxide narcosis. Nikethamide proved to be an efficacious respiratory stimulant, although its principal disadvantage was the relevant shortness of action. The maximum effect of intravenous injection occurred between 10 and 20 minutes and of intramuscular injection between 30 and 45 minutes. Despite this, in most cases the boost given by this drug to the respiratory centre was necessary only at 2-hourly intervals. Amiphenazole was used in the more seriously affected patients. Its effect upon respiratory depression appeared to be minimal and it is doubtful whether it contributed to the success of treatment.

Prognosis

It is evident from the review of patients admitted before 1957 that the prognosis of anoxic cardiac failure in pulmonary heart-disease is poor. In a series of fifty patients with pulmonary heart-disease Fulton (1953) found that once œdema had appeared 18% died within 48 hours of admission, 37% within 1 month, and 100% within 2 years. In this review 16% died within 48 hours and 38% within 1 month. He and other workers, however, had not noted the greatly increased mortality-rate amongst patients in whom right-ventricular strain appears in the E.C.G. Fourteen of the nineteen patients who showed this abnormality died in hospital, eight of these within 4 days of admission. It was during this period that the patients treated by continuous oxygen and respiratory stimulants showed the most striking improvement in prognosis.

With optimum treatment by adequate oxygenation most, if not all, patients with acute anoxic cardiac failure can be tided over the initial acute period and be given the opportunity of recovering their cardiorespiratory equilibrium. Each fresh respiratory infection, however, adds further permanent damage to lung tissue, and it is to be expected in a patient with a severely impaired respiratory reserve that eventually one further infection will kill him. Thus it is not surprising that the prognosis in the two groups after the 5th day is similar. Possibly the full importance of vigorous initial hospital treatment has not been appreciated in the past.

Anoxia and Renal Function

Renal plasma-flow and glomerular filtration-rate are known to be impaired in pulmonary heart-disease with cardiac failure (Davies and Kilpatrick 1951, Fishman et al. 1951, Lewis et al. 1952). Oliguria and even anuria are known to occur (Black and Stanbury 1958). It is doubtful, however, whether the frequency and duration of renal impairment in anoxic cardiac failure are widely recognised.

In all patients in this series definite oliguria persisted for 5–15 days after admission, the average being 8 days. Furthermore there was an increase in œdema during the initial 3–10 days of treatment when obvious clinical improvement was taking place in most patients. This was in no way associated with the duration of continuous oxygen therapy, nor did it parallel the administration of respiratory stimulants. Rather it appeared to be associated with disappearance of the characteristic high-output state and the increase in blood-volume associated with this (Lewis et al. 1951).

Thus œdema must develop when vasodilation regresses and blood-volume returns to normal, unless a diuresis occurs. It appears that the "anoxic kidney" even after relief of anoxia takes time to recover. This delay in recovery coincides with a reduction in blood-volume and results in an increase of œdema which becomes maximal shortly before the onset of diuresis. Histologically there is no definite pathological change in renal parenchyma during this period (Simpson 1957) and this is therefore apparently a functional disturbance; further anoxia during this period, however, may lead to more permanent renal damage with overt tubular necrosis (case 4).

These findings suggest that oxygen therapy should be continued at least until a diuresis has begun.

This series is too small to assess accurately the value of diuretics. On half the occasions used they appeared to initiate a diuresis, but in the less seriously ill patients who were not given diuretics a spontaneous response took place at a similar interval after starting treatment. On the whole diuretics seem to be of value once the functional renal disturbance has recovered.

There were definite E.C.G. changes in only five instances following therapy and the significance will be discussed in a later paper (Kellaway 1959).

It has been said that once cardiac failure has developed the prognosis in pulmonary heart-disease is so poor that most patients die within 2 years, and that many of these patients are respiratory cripples during that period (Fulton 1954). The inference is that energetic treatment of these patients is perhaps not justified in view of such disappointing results. Follow-up of the patients in this series revealed that half the eighteen patients have died but of the remaining nine patients four have returned to their original occupations, two after an interval of 2 years. Of the remaining five patients two only are severely hampered by respiratory insufficiency. Thus with full oxygenation and energetic early treatment of anoxic cardiac failure not only the immediate prognosis, but also the ultimate outlook, of such patients is considerably bettered.

Summary

Pulmonary heart-disease is one of the major causes of congestive cardiac failure in Britain. In three hundred and thirty-four patients admitted to hospital with cardiac failure it occurred, uncomplicated by other cardiovascular disease, in 15% of the subjects. Of those with acute anoxic cardiac failure who showed right-ventricular strain electrocardiographically three-quarters failed to survive. The initial 4 days in hospital proved critical for these patients.

While antibiotics help overcome the respiratory infection the essential problem is to relieve anoxia without permitting carbon-dioxide narcosis to supervene. Apart from treatment with mechanical respirators there is no readily available method of restoring arterial oxygen levels to normal without this danger.

A method of administering continuous oxygen therapy whilst avoiding carbon-dioxide intoxication by the regular administration of respiratory stimulants is outlined and the results of this treatment, in particular the improvement in prognosis, are recorded.

Oliguria persists for several days after arterial oxygen saturation has been raised to normal levels. During this

period œdema increases despite clinical improvement. The results suggest that oxygen should be continued until diuresis begins.

The absence of deaths due to carbon-dioxide narcosis and the improvement in immediate and more distant prognosis suggest that this is a good method of managing these patients.

I thank Dr. A. Rae Gilchrist for his interest and encouragement in the preparation of this paper. I am very much indebted to the staff of the cardiology department for their help in the practical management of the patients.

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Reviews of Books

Principles and Practice of Obstetric Anæsthesia

J. SELWYN CRAWFORD, M.B., D.A., F.F.A. R.C.S., anæsthesia service, Presbyterian Hospital, New York; late first assistant, department of anæsthesia, Central Middlesex Hospital, London. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 128. 20*s*.

IN writing this book Dr. Crawford has filled a gap in British medical literature, for there has for several years been no up-to-date work on this subject. In two brief but factual and well-referenced chapters he has summarised present-day knowledge of maternal and placental physiology in relation to anæsthetic drugs and procedures, and used these as the basis for later chapters on analgesic and anæsthetic methods during pregnancy and labour. The approach to analgesia is a welcome appraisal, and recommendation, of such drugs as the phenothiazine derivates and opiate antagonists, in combination with those of established repute, like pethidine. The anæsthetic sections, though they contain much information, are not always easy to follow and occasionally commend some unsound practices. The work is completed by chapters on the child, equipment and administration, and a thoughtful epilogue on the future of obstetric anæsthesia.

Dr. Crawford has a sincere regard for the useful part an experienced anæsthetist can play in obstetrics, and he has not failed to remark on the relative failure in this respect of the anæsthetic services in this country. This is a thought-provoking book that will be read with interest by both obstetricians and anæsthetists.

Eat Well and Stay Well

ANCEL and MARGARET KEYS. New York: Doubleday. 1959. Pp. 359. $3.95.

THE view that there is some connection between atheroma of the coronary arteries, the concentration of cholesterol in serum, and the type and amount of fat in the diet is widely held. The ratio of saturated to unsaturated dietary fat appears to be an important factor. Among those who have contributed to our knowledge of the subject, Ancel Keys has been outstanding, both in field surveys in various parts of the world and in the laboratory.

Under pressure from physicians and patients, he and his wife have now restated the case for reducing the amount of fat, and particularly the saturated fat, in the diet of those with access to unrestricted food-supplies. The book opens with a frank discussion of the evidence on which the recommendations are based, and the authors are careful to point out that dietary fat may represent only one of several important influences leading to the eventual appearance of ischæmic heart-disease. They add that, even if the role of fat is limited, we should not be deterred from tackling this aspect of the problem, which to some extent is amenable to control. In a section dealing with obesity, their view is that " getting fat is basically simply a matter of calories " and that " the cause of obesity is too much food, too little exercise, or both ". The advice offered is probably unnecessarily complex, and would therefore discourage many patients (particularly the suggestion that a calorie balance should be established before embarking on a reducing regimen, so that an estimate can be made in advance of the energy requirements to provide a predictable rate of weight loss).

The largest section of the book consists of complete menus, with appropriate recipes, for one week in each of the four seasons, at levels of 1800 and 2300 calories per day, each designed to maintain a low intake of fat, especially saturated fat. The place of wines and other forms of alcohol has not been forgotten, and there are tables providing information for the nutritionist or cook who wishes to explore the possibilities of diets low in saturated fats beyond the menus and recipes already generously provided. The authors' studies have taken them to many parts of the world, and this is reflected in many of the dietary novelties they describe.

The book also contains advice directed at the dairy industry, the pig industry, and, by implication, the majority of the food industries. Dietitians should find it of particular interest. In view of the importance of the problem, the standing of the authors, and the controversial state of many of the issues raised, the book deserves the attention of all who find themselves concerned in one way or another.

Trends in Genetic Analysis

G. PONTECORVO, F.R.S., professor of genetics, University of Glasgow. New York: Columbia University Press. London: Oxford University Press. 1959. Pp. 145. 25*s*.

THOUGH it is based on the Jesup lectures given at Columbia University in 1956, Professor Pontecorvo's book does not give the impression of being out of date. For most people with some knowledge of classical genetics it will form a valuable refresher course in recent advances, or at least (for it does not pretend to be complete) in some of the directions in which genetic research is most active at present. Most important, and occupying in various guises most of the book, is the breakdown of the gene. The chromosome is no longer, in the author's metaphor, a

string of independent Chinese characters, but a length of hand-written English in which we are not even certain that the words are written separately; a mutation is a change in spelling, not a change of a whole ideograph: the particulate gene is replaced by the complex cistron. Much more briefly treated, but equally interesting, is a consideration of the methods of recombination available in the absence of true sexual reproduction: the transfer of genetic material that occurs in microorganisms is only one of these alternatives. Professor Pontecorvo's own work with fungi has shown that one such alternative, mitotic segregation in cultures, is a powerful tool of genetic analysis, and he suggests that, if the formidable technical difficulties can be overcome, its use in human tissue-cultures offers a short-cut approach to human genetic problems.

Surgery of the Colon

E. S. R. HUGHES, M.D., M.S., F.R.C.S., F.R.A.C.S., honorary surgeon, Royal Melbourne Hospital. Edinburgh: E. & S. Livingstone. 1959. Pp. 416. 63*s*.

Diseases of the Colon and Anorectum

Vols. 1 and 2. Editor: ROBERT TURELL, M.D., assistant surgeon and chief, Rectal Clinic, the Mount Sinai and Montefiore Hospitals, assistant professor of clinical surgery, Albert Einstein College of Medicine, New York. Philadelphia and London: W. B. Saunders. 1959. Pp. 1308. £12 15*s*.

Mr. Hughes has written a highly personal book reflecting his interests. The cognoscenti can skip the traditional opening, with surgical anatomy followed by methods of investigation, and pass to the anecdotal and certainly more lively chapter on chronic constipation, where the satisfactions of modern plumbing have not been overlooked (it is a pity that Reynolds on the History of the Water Closet has been omitted from the bibliography!). In the next chapter, diarrhœa is discussed, first in general terms, then as presented in all forms of colitis. Colitis and tumours of the colon form the core of the work, though a whole chapter is devoted to large-bowel obstruction, where cæcostomy versus colostomy forms the chief point of discussion with, as in so many works like this, no clue to mortality. Diverticulitis, amœbiasis, and endometriosis all find a place in a book that is easy to read and has an individual quality.

In contrast Dr. Turell's book has an impersonal quality expected when no less than 82 experts (3 of them British) have been asked to contribute; but it is authoritarian, and, despite its size, readable. The first volume is mainly devoted to all the facets of large-bowel cancer after the usual but by no means conventional preliminary chapters on embryology, anatomy, physiology, endocrinology, biochemistry, nutrition, and chemotherapeutics. The second volume starts with a perceptive discourse on intestinal obstruction (again no mortality statistics), then moves to inflammatory and ulcerative lesions, thence to functional disorders including constipation (this time without reference to plumbing). Not even the appendices epiploicæ are forgotten. After a section on the anal region, the first part contains a miscellany of special features.

Most sections are written with a depth and clarity that is wholly commendable and gives the book a highly professional air. The illustrations are excellent. It will inevitably become the work of reference to which all interested in the subject will turn.

Systemic Lupus Erythematosus

Editors: GEORGE BAEHR, M.D., PAUL KLEMPERER, M.D. London and New York: Grune & Stratton 1959. Pp. 84. 27*s*.

THIS symposium contains six articles on different aspects of systemic lupus erythematosus by authors who are or have been on the staff of the Mount Sinai Hospital, New York. Abou B. Pollack discusses the pathology and the relation of the findings to the "auto-immune" theory of its causation, about which he hardly seems convinced. G. C. Godman collects the remarkable amount of information that now exists about the L.E.-cell phenomenon. This subject is also dealt with by Lee and Davis, and they add discussion of biochemical, cellular, and other changes in the blood. Saul Jarcho deals briefly with the clinical features and the many difficulties of diagnosis; he points out that the L.E.-cell test rarely yields a false positive and has therefore been most valuable; he also mentions the odd mimicry of systemic lupus erythematosus produced by toxic reaction to hydrallazine ('Apresoline'). Gribetz and Henley review the few reported cases of the disease in children under 15 and point out that the disease differs little from that in the adult. Finally, Louis J. Soffer considers the practical aspects of steroid therapy, which allows control but not cure. Although he mentions most of the newer steroids, he does not express strong preference for any one of them. Each chapter has its own bibliography (Soffer contents himself with 16 references, Godman cites 137). This monograph provides a very useful, but inconclusive, survey of present knowledge of this puzzling disease.

Group Psychoanalysis

B. BOHDAN WASSELL, M.D. London: Peter Owen. 1959. Pp. 306. 30*s*.

THIS book will interest psychiatrists who practise group psychotherapy, but its claim, in the author's introduction, to provide "in the first several chapters" something easily digestible by the intelligent layman may be questioned. Dr. Wassell is an enthusiastic follower of Karen Horney, and sees his patients' neuroses and their cure in terms of cultural adjustment. He emphasises throughout the tendency for the neurotic to develop false modes of conforming to society, from infancy onwards, and how it is the task of the analyst and the group to enable him to find his real self and come to terms with society on a realistic footing.

Little is made of the therapeutic effect of the group members upon each other, and the analyst is correspondingly regarded as almost the sole source of insight and cure; but the chapters on technique and the handling of specific problems contain much that is valuable. The book suffers from a somewhat florid style, and the case-histories illustrating technical points are at times too discursive.

Primer of Water, Electrolyte and Acid-Base Syndromes

EMANUEL GOLDBERGER, M.D., F.A.C.P., lecturer in medicine, Columbia University, New York. London: Henry Kimpton. 1959. Pp. 322. 45*s*.

THIS book is hardly a primer: the pages are filled with detailed examples, with lists, and with cook-book information; and it is hard to find any coherent account of the principles of approach. The arrangement is Procrustean, with burns appearing as a sodium-loss syndrome, and renal failure, diabetic ketosis, and salicylate poisoning as metabolic-acidosis syndromes. Principles of treatment are given 3 pages, but there are 24 pages on available solutions. There is much correct information in this book, and it can be extracted by using the index; but it cannot be recommended as an introduction to the subject.

Current Therapy 1959 (Philadelphia and London: W. B. Saunders. 1959. Pp. 781. 84*s*.).—This popular annual, edited by Dr. Howard F. Conn, is now entering its second decade. This year there are contributions from over 400 American physicians, among them many famous names. Of unusual interest is the section on physical and chemical injuries, and there are detailed tables of the poisonous constituents of a great many domestic and industrial products. There are also lists of drugs under their American names with details of dosage for children, and useful conversion tables for the metric and apothecaries systems. A table of normal laboratory values is now an indispensable feature of any medical textbook, and a good one is included here. For 4 guineas a year this is an admirable means of keeping up to date, and it is just the book for rapid reference in hospital libraries.

THE LANCET

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Experiments with Lymphocytes

FOR many years there has been controversy over the function, site of production, life-cycle, and life-span of the lymphocytes. By labelling cells with isotopes, OTTENSEN [1] found that the life-span of granulocytes was 9–13 days; lymphocytes were of two types—those with a mean age of 3 to 4 days, and a more numerous long-lived group with a mean age of 100–200 days. In chronic lymphatic leukæmia CHRISTENSEN and OTTENSEN [2] and others have estimated the mean life of the lymphocyte at about 200 days. But such a long life-span of the lymphocytes is difficult to reconcile with experimental work in this country, particularly by YOFFEY and his coworkers at Bristol. This work showed that very large numbers of lymphocytes enter the blood daily via the thoracic duct and other communications between the lymphatic and venous systems; YOFFEY et al.[3] have estimated the daily replacement factor in the guineapig at 8 times, and HUGHES et al.[4] put the figure at 11 times in the rabbit. Another difficulty is that transfused lymphocytes rapidly disappear from the circulating blood, and according to YOFFEY most of them go into the bone-marrow. If the life-span of the lymphocyte is so long, accumulation of lymphocytes in the bone-marrow would be expected, and YOFFEY et al. have in fact calculated that "for every lymphocyte normally in the circulation, 3 are daily entering it via the thoracic duct and 23 are in the bone marrow". All these calculations assume that enough *new* lymphocytes are produced in the lymphoid tissue to enter the thoracic duct and that cells in the bone-marrow and the blood do not recirculate to any significant extent. One explanation, favoured by YOFFEY [5] and by others, is that the lymphocytes in the bone-marrow can act as "blast cells" capable of differentiation into other cell types, including erythroblasts.

PERRY et al.[6] have recorded the results of studying in the dog the uptake and release of ^{32}P by lymphocytes. Some animals were given ^{32}P intravenously, and then lymphocytes were collected from the thoracic duct; in other animals peripheral blood was collected at intervals after ^{32}P administration and the lymphocytes and granulocytes were separated.[7] In other experiments lymphocytes were labelled with ^{32}P in vitro. The rate of appearance of ^{32}P incorporated in desoxyribonucleic acid (D.N.A.) and ^{32}P specific activity were determined by published methods. They found that D.N.A.-^{32}P-labelled lymphocytes could be detected in the thoracic duct two hours after giving ^{32}P, and were probably present earlier since quite a lot of cells must be present to be detected by the technique used; the peak of activity was reached in 6–8 hours and fell off quickly, but was still detectable 160 hours later. Lymphocytes appeared in the thoracic duct at the rate of 430 million per hour—enough to replace the circulating lymphocytes 7 times a day. In the blood the peak of lymphocyte activity did not appear until the 4th day, at the same time as the peak for granulocytes. In the lymphocytes incubated with ^{32}P, incorporation with D.N.A. occurred very quickly, and similar in-vitro activity could be induced in lymphocytes in a chylous fluid from a human patient. When these in-vitro labelled lymphocytes were injected intravenously into the donor dogs, radioactivity appeared in the bone-marrow within 15 minutes, reached a peak in 2 days, and then fell off in the next 10 days; labelled lymphocytes were at a maximum in the blood on the 5th day. In one experiment thoracic-duct lymph was collected after the injection, but no labelled lymphocytes had appeared in 3 hours.

PERRY and his colleagues note that their results again confirm the remarkable flow of lymphocytes in the thoracic duct. But two points are surprising: the cells require only a very short time (less than 2 hours) for D.N.A.-^{32}P incorporation; and the in-vitro experiments show that incorporation of D.N.A.-^{32}P is not, as had been thought, limited to cells which will later undergo mitosis; this must mean, they say, "that lymphocyte growth, maturation and division occur not only at the site of origin, i.e., in the lymphoid tissue, but during the period of transport to the blood as well;" indeed even lymphocytes in the circulating blood seem capable of a low level of D.N.A. synthesis. These findings greatly complicate the interpretation of isotope data, and it does not seem that the data obtained so far enable the lymphocyte's life-span to be firmly estimated; it may well be shorter than expected, and the older estimates of a few days may be nearer the mark.

The observation by PERRY et al.[7] that lymphocytes and granulocytes show a simultaneous peak of D.N.A.-^{32}P activity on the 4th day can be interpreted as supporting the idea that lymphocytes, after entering the blood from the lymphatic vessels, quickly enter the bone-marrow and are then released simultaneously with the segmented neutrophils. PERRY et al. state that they do not know what proportion of lymphocytes entering the marrow actually leave again, and they suggest that determination of this figure, coupled with radio-autographic histological techniques, should shed light on the disputed question of whether the lymphocyte is a multipotential cell.

Another interesting set of experiments is concerned with the changes that lymphocytes undergo in inflammatory exudates. REBUCK and CROWLEY [8] devised a simple technique for studying the progressive cellular changes.

A small area of skin on the forearm or thigh is scraped to a depth of about 1 mm.; a coverslip is fixed in place over the area and removed after a suitable period, when a fresh coverslip is put in place; in this way a succession of preparations showing changes throughout the inflammatory cycle is obtained.

1. Ottensen, J. *Acta physiol. scand.* 1954, **32**, 75.
2. Christensen, B., Ottensen, J. *Acta hæmat.* 1955, **13**, 289.
3. Yoffey, J. M., Hanks, G. A., Kelly, L. *Ann. N.Y. Acad. Sci.* 1958, **73**, 47.
4. Hughes, R., May, A. J., Widdicombe, J. G. *J. Physiol.* 1956, **132**, 184.
5. Yoffey, J. M. *J. Histochem.* 1956, **4**, 516.
6. Perry, S., Craddock, C. G., Jr., Paul, G., Lawrence, J. S. *Arch. intern. Med.* 1959, **103**, 224.
7. Perry, S., Craddock, C. G., Jr., Ventzki, L., Crepaldi, G., Lawrence, J. S. *Blood*, 1959, **14**, 50.
8. Rebuck, J. W., Crowley, J. H. *Ann. N.Y. Acad. Sci.* 1955, **59**, 757.

They found that at first neutrophil polymorphs are practically the only cell present; after 9 hours a considerable number of lymphocytes appear and the granulocytes begin to degenerate. At 12 hours the lymphocytes are more numerous and larger types are seen; between 12 and 18 hours the lymphocyte nuclei enlarge and may become indented, and the chromatin pattern is finer. At 24 hours the cells are mostly large mononuclears with the nuclei of early macrophages and histiocytes. BRAUNSTEINER et al.[9] have repeated these experiments with similar results, and note that the cells in preparations made later than 18 hours after the lesion are so different that it is difficult to appreciate that they began as lymphocytes; they may be up to 16 μ across and have multiple nuclei, while others have large " monocytoid " nuclei. To confirm the lymphocytic origin of these late cells BRAUNSTEINER et al. utilised the observation of LAWRENCE[10] that lymphocytes will transfer " delayed allergy " in man: for example, transfer of about 0·1 ml. of lymphocytes from a patient with a positive tuberculin skin reaction to a patient who is tuberculin-negative will convert this reaction to positive. They used for their experiments 3 patients who had had tularæmia and were sensitive to tularin, and 1 patient who was tuberculin-positive. Coverslip preparations from experimental inflammatory lesions on these patients were obtained after 18–24 hours; the cells were removed, and 20–30 million cells were transferred to suitable tularin-negative and tuberculin-negative patients. Each recipient showed a definite positive reaction after 2–4 days; there were no changes in serum-agglutination titres. These cells from the inflammatory exudate showed what " at present . . . is the only physiologic activity of lymphocytes we know of ". Thus the cellular defence against inflammation or injury has three aspects—immediate phagocytic activity by granulocytes and later by monocytes, antagonistic substances provided by lymphocytes and cells derived from them, and circulating antibodies in plasma.

Despite extensive work on the lymphocytes, there is still little certain knowledge. Much of the information is derived from studies on rodents, and there has always been some doubt about how far these results apply to man or other mammals. We are glad to see that the experiments discussed here have been made with human or canine cells.

Thyrotoxic Heart-disease

THE association of heart-disease with thyrotoxicosis is undisputed, but the relation of the one to the other is still debated. All patients with appreciable thyrotoxicosis show circulatory abnormalities consisting of tachycardia, hyperdynamic bounding pulse, wide pulse-pressure, systolic hypertension, and moist warm extremities; the cardiac output is increased, and the venous pressure raised. The overactive slapping left ventricular impulse, and the presence of systolic ejection murmurs, suggest organic heart-disease. Pulmonary hypertension results from the high pulmonary flow[1] and accentuates the pulmonary closure sound. These signs are usually found in younger patients with diffuse toxic goitre and sinus rhythm. The hæmodynamic picture may be fairly ascribed to the circulatory effects of excessive thyroid hormone, for it reverts to normal when the thyrotoxicosis is controlled or cured, and resembles that in any condition which produces a high output or hyperdynamic cardiac state, such as severe anæmia, hepatic disease, cor pulmonale, and arteriovenous fistula. Indeed, when the thyroid gland is extremely large and vascular it may be regarded as an arteriovenous communication, and not unusually a continuous murmur can be heard over it. In older patients with thyroid intoxication, serious heart-disease with atrial fibrillation, cardiac enlargement, and true congestive heart-failure is common.

FRIEDBERG and SOHVAL[2] argued that thyrotoxicosis produces true cardiac failure only when there is other heart-disease, but many others have maintained that thyrotoxicosis alone can be responsible.[3 4] Further light has been shed on this question in an important paper by SANDLER and WILSON,[5] who have studied 462 patients with thyrotoxicosis, of whom 150 had cardiac involvement. These were divided into two groups: (1) 86 (57%) with other heart-disease of various types; and (2) 64 (43%) without other heart-disease. The patients with cardiac involvement were in the older age-groups, but no significant difference was found between those with and those without other heart-disease in respect of severity, duration, or results of therapy with ^{131}I, nearly 60% becoming euthyroid after a single dose.

Other heart-disease consisted of ischæmic, hypertensive, rheumatic, pulmonary, and congenital disorders. Of the 43 patients with cardiac ischæmia, 21 had angina, which improved after ^{131}I therapy in 19, 10 being completely relieved of pain. All but 9 of these 21 patients were female, indicating the importance of suspecting associated thyrotoxic heart-disease in female patients with angina. Apparently no thyrotoxic patient had angina without underlying ischæmic disease.

Of the 64 patients without other heart-disease, 48 had atrial fibrillation, 26 congestive heart-failure, and 13 cardiomegaly alone. All but 3 of the 26 patients with heart-failure had atrial fibrillation; but the fact that 16 patients had cardiac involvement with sinus rhythm suggests that true thyrotoxic heart-disease can arise in the absence of arrythmia and that cardiac enlargement cannot necessarily be ascribed to atrial fibrillation. (SANDLER and WILSON do not distinguish between paroxysmal and established fibrillation in their cases; and the former, which is known to occur in thyrotoxicosis, might possibly give rise to cardiac enlargement.)

Atrial fibrillation occurred in 42% of the patients with, and in 75% of those without, other heart-disease, but the prevalence increased progressively with age in the whole series. Spontaneous reversion to sinus rhythm after treatment with ^{131}I was commoner in the younger and in male patients than in the older and in females. Neither the duration of the thyrotoxicosis nor the severity or type of goitre was related to the presence or absence of sinus rhythm or the rate at which

9. Braunsteiner, H., Paertan, J., Thumb, N. *Blood*, 1958, **13**, 417.
10. Lawrence, H. S. *Amer. J. Med.* 1956, **20**, 428.

1. Humerfelt, S., Müller, O., Storstein, O. *Amer. Heart J.* 1958, **56**, 87.
2. Friedberg, C. K., Sohval, A. R. *ibid.* 1937, **13**, 599.
3. Griswold, D., Keating, J. H., Jr. *ibid.* 1949, **38**, 813.
4. Cookson, H. *Brit. med. J.* 1959, i, 254.
5. Sandler, G., Wilson, G. M. *Quart. J. Med.* 1959, **28**, 347.

the rhythm spontaneously reverted to normal. Congestive heart-failure was found in 35% of patients with other heart-disease, and in 41% of those without, and it was commoner in the older patient. 40% of patients in both groups obtained complete relief of failure with treatment for thyrotoxicosis alone, and about 20% of each group died in heart-failure. Cardiomegaly was diagnosed on radiological and cardiographic grounds in 13 patients in the absence of atrial fibrillation, congestive heart-failure, or other disease. The cardiographic evidence, however, was not striking, although X-rays apparently showed definite cardiac enlargement. Necropsy was carried out in 9 patients in the series. Of 6 patients without other heart-disease, 4 had biventricular hypertrophy: right-ventricular hypertrophy was present in 1, but there was no cardiac enlargement in the 6th patient. Patchy myocardial fibrosis was present in 1, but the coronary arteries were only slightly atheromatous. SANDLER and WILSON conclude that the incidence of all thyrotoxic cardiac complications increases with age, as does hypertension and coronary-artery disease, but that severe cardiac complications can develop with very slight hypertension and healthy coronary arteries, so that, at least in the elderly, thyrotoxicosis alone can cause serious cardiac damage. This is perhaps not unexpected; for myocardial damage and cardiac enlargement can be induced in rats by the administration of thyroid extract.[6]

SANDLER and WILSON's cases were treated with ^{131}I, and the results are of great interest. In about a third of the patients with atrial fibrillation sinus rhythm was restored; where congestive cardiac failure was present, such reversion was less likely. The reversion-rate was higher in the younger patients and in males. Over half the patients with congestive heart-failure had no recurrence, and more than a third did not need subsequent specific cardiac therapy. As might be expected, patients with atrial fibrillation improved more if sinus rhythm had been restored. Cardiac enlargement unassociated with heart-failure or atrial fibrillation did not regress after therapy even when there was no apparent cause other than thyrotoxicosis—suggesting that the cardiomegaly was not merely the result of the toxic goitre acting as an arteriovenous fistula.

Clearly thyrotoxicosis can cause serious heart-disease in older persons even in the absence of an underlying cardiac disorder, and effective treatment of the thyrotoxicosis can dramatically improve cardiac function even in the presence of associated cardiac disease. SANDLER and WILSON's results show that treatment with ^{131}I is effective, and is certainly the method of choice for the elderly thyrotoxic patient with heart-disease, unless local effects of the goitre or toxic adenoma demand operation. The failure of some patients to revert from atrial fibrillation to sinus rhythm is presumably related to associated cardiac disease and to age. The conversion-rate with ^{131}I is of the same order as that obtained by GOODWIN [7] with the earlier anti-thyroid drugs of the thiouracil series, and by ERNSTENE [8] after partial thyroidectomy—although GRISWOLD and KEATING [3] reported a 50% conversion-rate after this operation. SANDLER and WILSON's paper, besides indicating the value of effective treatment in thyrotoxic heart-disease, emphasises the importance of looking for masked thyrotoxicosis in elderly patients with cardiac failure who do not respond to treatment in the expected fashion.

6. Hashimoto, H. *Endocrinology*, 1921, **5**, 579.
7. Goodwin, J. F. *Brit. med. J.* 1949, i, 895.

The Sex of Teratomas

THERE has been a good deal of resistance to the view that some teratomas in males are female; and indeed this view could not be accepted without reserve so long as it depended on nuclear sexing alone. The report by Dr. GALTON and Dr. BENIRSCHKE on an earlier page of this issue represents a first attempt to settle the issue by chromosome studies.

In their nuclear sex the cells of the great majority of tumours follow that of the host; but where the nuclei are notably pleomorphic the sex chromatin is not easily recognised, and in any case the chromosomal irregularities which lie behind nuclear pleomorphism would be expected to lead to difficulties in interpretation. TAVARES [9] reported some curious findings in undifferentiated tumours; but in well-differentiated tumours, benign or malignant, the sex is usually clear. In teratomas in females, almost all observers agree that the nuclear sex of the cells is constantly female. In males, however, apparantly about half are male and about half female. For testicular teratomas at least, this may be taken as established.[10–13] It is not so certain for teratomas elsewhere: the pineal teratoma of HUNTER and LENNOX's [10] original series is now known to have arisen in a case of chromatin-positive Klinefelter's syndrome (an unrecognised condition at that time), and this possibility has, so far as we know, not been altogether eliminated in the two other recorded cases.[14 15] If the anomaly of sex is confined to the testis, or even if it is only very much commoner there than in extratesticular teratomas, the original explanations of HUNTER and LENNOX and of TAVARES [11] for these findings—that teratomas arise from haploid cells (a pair being assumed to fuse according to one explanation, and a single haploid cell to reduplicate its chromosomes according to the other) are much easier to accept, since haploid cells are normally present in the testes as part of the process of spermatogenesis. Since all the haploid cells of a female must be X, clearly only XX diploid cells can arise from them; but since the male haploids may be X or Y, whatever the exact mechanism of production of a diploid cell from them, an XX is among the possible products. A testicular teratoma—and presumably equally an ovarian teratoma—is according to this reasoning a kind of parthenogenetic offspring of the germ cells.

A major assault on this view has recently been made

8. Ernstene, A. C. *Amer. J. med. Sci.* 1939, **195**, 248.
9. Tavares, A. S. *J. Path. Bact.* 1957, **74**, 25.
10. Hunter, W. F., Lennox, B. *Lancet*, 1954, ii, 633.
11. Taveres, A. S. *ibid.* 1955, i, 948.
12. Moore, K. L., Barr, M. L. *Brit. J. Cancer*, 1955, **9**, 246.
13. Ashley, D. J. B., Theiss, E. A. *Science*, 1958, **128**, 434.
14. Cruickshank, D. B. *Lancet*, 1955, i, 253.
15. Myers, L. *J. Path. Bact.* 1959, **78**, 43.

by Dr. LOIS MYERS[15 16] using the large teratoma collection of Prof. R. A. WILLIS. In most respects this exceptionally detailed and painstaking study confirms the views already outlined. Two points of doubt emerge, however. In the first place, the ductuli efferentes of the testis were found to have a high sex-chromatin count (56%), which raises the rather remote possibility that teratomas may arise from this source. Secondly, the position with regard to testicular teratomas was found to be more complex than had been thought. Of 33 such cases, 13 were uniformly male and 10 uniformly female; but 8 were mosaics, consisting of a mixture of male and female tissues, and 2 showed *double* sex chromatin in nearly half their nuclei. Previous workers, faced with a mosaic case, would almost certainly have called the teratoma female, and assumed that the areas in which the sex chromatin could not be seen were simply the result of patchy fixation and similar technical difficulties; but MYERS gives good reason for believing that the mosaics she has observed are genuine. She believes that these findings invalidate the parthenogenesis theory, and suggests several cytological mechanisms by which the sex chromatin might appear in the cells of teratomas as a kind of artefact. This, though possible, does not explain why these artefacts are found in teratomas but not in other tumours. The mosaic teratomas (though not the double-sex-chromatin ones) can after all be explained on the parthenogenesis theory on a basis of origin from a group of cells, rather than a single cell.

Such arguments, however, are sterile now that the actual chromosomes which produce these cytological anomalies can be studied. GALTON and BENIRSCHKE describe a metastasising teratoma of the ovary, female on nuclear sexing, with a normal female chromosome count. It is a pity that it had to be an ovarian tumour, for the real argument centres on the testicular tumours. But what applies to one may well apply to the other. If once it is established that a single testicular teratoma has likewise 46 chromosomes and an XX pair, most of MYER's objections will be overcome. Let us hope that one of the many teams now turning to human chromosome work will soon be able to determine the status of testicular teratomas.

16. Myers, L. *ibid.* p. 29.

Annotations

ANOTHER BOXING DEATH

TWICE in the past two years the mention in our columns[1] of the death in England of a boxer has been the starting-point of a controversy, extending once to the House of Commons, in which the supporters of boxing, lay and, alas, medical, have assured us that the hazards of the "sport" are negligible. Yet the facts continue to tell another story. On Oct. 26 a Californian bantam weight died in Mexico from cerebral hæmorrhage two days after a contest with the world champion Jose Becerra.[2]

This latest death coincided with a discussion at the Medical Society of London on the hazards of boxing—a choice of subject which suggests that the profession continues to be concerned about its undeniable responsibilities in this matter. In this latest discussion little fresh ground was broken, but after several graphic descriptions of punch-drunk pugilists it became clear that the audience had little disposition to defend professional boxing either as a worth-while sport or as a civilised spectacle. One of the difficulties in assessing exactly the damage which boxing does to the brain derives from the paucity of pathological material; but in the few cases studied post mortem gross atrophy of the cerebral cortex has been noted, and a pathologist at the meeting took the opportunity of appealing for brains from punch-drunk boxers.

If professional boxing found no advocates, opinion on the subject of amateur boxing was less unanimous. Some claimed that it is a wholly admirable character-building activity, free from material risk, and a useful safety-valve for aggressive instincts. Other speakers, however, dissented, questioning each of these claims with varying emphasis and doubting the wisdom, on either physical or moral grounds, of allowing growing boys to box. We share their doubts; for it seems illogical to assume that a sport which at the professional level can unquestionably produce a punch-drunk imbecile and—as we have again been reminded—occasional deaths can leave the amateur's brain unscathed. We hope that the time is coming when Britain will give the brain the benefit of any remaining doubt by following Iceland's example and declaring boxing illegal.[3]

1. *Lancet*, 1958, i, 907; *ibid.* 1959, i, 1185.
2. *Birmingham Post*, Oct. 27, 1959.

GENERAL PARALYSIS OF THE INSANE

Hahn and his colleagues[4] have published a valuable report on the penicillin treatment of G.P.I. based on 1086 cases collected from eight hospitals in the United States. The majority of the patients had been kept under observation for at least five years after the initial treatment, and the case-recording at the original admission and on subsequent examinations was standardised. The disease was three times as common in men as in women, and the usual incubation period was 10–24 years after infection with a spread of from 2 to more than 30 years. The simple dementing type of psychosis was considerably commoner than the manic expansive type or the type presenting as a depression. A negative blood Wassermann reaction was found in 8% of the 327 previously untreated patients, but the Wassermann reaction of the cerebrospinal fluid (C.S.F.) was always positive. No correlation could be found between the initial C.S.F. cell-count or protein content and clinical severity.

Hahn et al. found that early diagnosis and prompt penicillin treatment of incipient paresis produces clinical improvement and ability to work in more than 80% of patients, and nearly eliminates deaths from neurosyphilis. Even in severely affected patients needing treatment in a mental hospital there is a one in three chance of improvement and reablement for work. In very few cases, however, is recovery complete; impairment of judgment and insight and of speech usually persists. This study suggested that 6 million units of penicillin was adequate, and that repository penicillin was as effective as aqueous penicillin. Further courses of penicillin were indicated only if clinical improvement was followed by deterioration

3. Dungal, N. *Lancet*, 1959, Sept. 5, p. 293.
4. Hahn, R. D., Webster, R., Weickhardt, G., Thomas, E., Timberlake, W., Solomon, H., Stokes, J. H., Moore, J. E., Heyman, A., Gammon, G., Gleeson, G. A., Curtis, A. C., Cutler, J. C. *Arch. Neurol. Psychiat.* 1959, **81**, 557.

or if the C.S.F. cell-count was greater than 5 per c.mm. after the first post-treatment year. A febrile Herxheimer reaction occurred in 14·9% of 629 patients treated with penicillin alone, and in 5·8% there was a "clinical" Herxheimer reaction with exacerbation of the psychosis or the occurrence of epileptic attacks. One patient died as a result of a Herxheimer reaction, but in the other patients there was no evidence of permanent damage from the reaction. Such reactions were especially common in cases where the number of cells in the C.S.F. was considerably increased. "Clinical" Herxheimer reactions were definitely less common in patients treated with penicillin plus fever than in patients treated with penicillin alone.

The pre-treatment C.S.F. findings were of some value in forecasting the response to treatment. A notable increase in the cell count indicated an active inflammatory process which would improve with treatment, although there might be residual symptoms due to damage to the brain before treatment was applied. Absence of C.S.F. pleocytosis indicated a relatively static process less likely to be improved by treatment but also less likely to deteriorate. The C.S.F. protein value was of less prognostic significance.

ADAPTATION IN CALCIUM ABSORPTION

SURPRISINGLY little is known about the factors governing the absorption of calcium from the gut. Although it has been thought for many years that the pH of the intestinal contents must play some part, because of the relative insolubility of the salts of calcium phosphate in alkaline media, no convincing evidence has been forthcoming. In fact vitamin D is the only physiological substance which has been recognised as playing an important, perhaps essential, role in calcium absorption in man.

Nicolaysen and his team [1] have long claimed that improved absorption of calcium is part of the adaptation of the organism (particularly the rat) to calcium deprivation. They have shown that animals deprived of calcium can increase the proportion of dietary calcium absorbed and retained, so long as their intake of vitamin D is adequate. This is probably also true in man, at least to judge by the efficient absorption observed in communities where intake of dietary calcium is low [2]; but reduction in urinary excretion of calcium also figures in adaptation to low-calcium intakes,[3] and is probably the most important change in short-lived deprivation.

Some years ago, two independent groups, in this country and the United States, drew attention to the low fæcal calcium which may be found in sarcoidosis with hypercalcæmia,[4 5] and they implied, on this and other grounds, that these patients might be unduly sensitive to vitamin D and that their hypercalcæmia might be due to absorption of too much calcium. Jackson and Dancaster [6] now report some observations in hypercalcuria which may call for a fundamental reconsideration of the relationship between absorption and excretion of calcium.

Jackson has studied 4 cases of sarcoidosis, 2 of idiopathic hypercalcuria,[7] and 1 of acromegaly. The common feature of all these patients was that they excreted more than 400 mg. of calcium daily on a normal intake—a figure which most observers would regard as abnormal, though the normal limits of urine calcium on a free diet have never been precisely defined. All 7 patients were found to be in calcium balance on an average diet, despite their high urinary excretion, and the explanation in every case was that the net absorption of calcium from the gut was abnormally high. Low-calcium diets, however, had little or no effect upon urinary calcium output, indicating that the urinary excretion could not be the result of the high rate of absorption. There seemed to be, in fact, a high and inevitable loss of calcium in the urine in these cases, suggesting the "endogenous factor" in urine calcium control previously postulated by Knapp [8] and Nicolaysen et al.[1]

Since absorption did not cause the hypercalcuria, Jackson and Dancaster suggest that the hypercalcuria may cause the high rate of absorption. In fact they postulate that the improved absorption represents an adaptation mechanism to the high output which enables the subjects to remain in positive balance. They apply this concept to both sarcoidosis and idiopathic hypercalcuria, and also (with perhaps less justification) to the favourable effect of vitamin D upon calcium absorption, which they think may be secondary to its effect on urine calcium.

These views are challenging but reasonable. The adaptation mechanisms are poorly understood, but their elucidation has been carried a great step forward by the patient work of Malm,[9] who has shown by prolonged calcium balances (extending over years) that although many individuals can adapt to low calcium intakes, some are unable to do so. Improved absorption of calcium is one of the mechanisms of adaptation in the patients he studied, and the implication is that patients who do not adapt must remain in negative calcium balance and presumably develop osteoporosis.[10] This possibility is also suggested by Jackson and is undoubtedly in the minds of many workers at present.

DESCENT OF MAN

IN 1871 Darwin suggested that man's evolutionary line ran from "forms very low in the mammalian series" through "progenitors of the existing Lemuridæ" and the catarrhine monkeys of the Old World, after these had diverged from the platyrrhine monkeys of the New World. All Darwin had to go on was the comparative anatomy of existing species and the assumption that anatomical resemblances indicate genetic affinity. This assumption was complicated (after Darwin's time) by the recognition of parallel evolution, pædomorphosis, and the production of apparently identical characters by different genetic mechanisms.

It is therefore appropriate that, at the centenary of Darwin's publication of his theory of evolution in his *Origin of Species*, Sir Wilfrid Le Gros Clark, in his Condon Lectures,[11] shows how Darwin's suggestion has been amply confirmed by the study of fossils discovered since his time and by the precipitin reaction, which indicates a close relationship between man and the anthropoid apes, a less close one with the catarrhine monkeys, and a distant one with the lower primates.

The fossil men that have been found range chronologically from Pithecanthropus to the South African Australopithecus. The lower miocene apes of East Africa

1. Nicolaysen, R., Eeg-Larsen, N., Malm, O. J. *Physiol. Rev.* 1953, **33**, 424.
2. Hegsted, D. M., Moscoso, I., Collazos, C. C. *J. Nutr.* 1952, **46**, 181.
3. Walker, A. R. P., Fox, F. W., Irving, J. T. *Biochem. J.* 1948, **42**, 452.
4. Henneman, P. H., Dempsey, E. F., Carroll, E. L., Albright, F. *J. clin. Invest.* 1956, **35**, 1229.
5. Anderson, J., Harper, C., Dent, C. E., Philpot, G. R. *Lancet*, 1954, ii, 720.
6. Jackson, W. P. U., Dancaster, C. *J. clin. Endocrin.* 1959, **19**, 658.
7. Henneman, P. H., Benedict, P. H., Forbes, A. P., Dudley, H. R. *New Engl. J. Med.* 1958, **259**, 802.
8. Knapp, E. L. *J. clin. Invest.* 1947, **26**, 182.
9. Malm, O. J. Calcium Requirement and Adaptation in Adult Men. Oslo, 1958.
10. Nordin, B. E. C. *Brit. med. J.* 1958, i, 1415.
11. The Foundations of Human Evolution. Published by Oregon State System of Higher Education, Eugene, Oregon, U.S.A. 1959.

also provide evidence of man's origin in that they show incipient brachiation, and Sir Arthur Keith showed that the posture related to brachiation was a prerequisite of the erect bipedal posture of man. Thus, as Australopithecus confirms the hypothesis that man is derived from an ancestral stock of the anthropoid apes, so the lower miocene apes of East Africa confirm the hypothesis that the anthropoid apes are derived from cercopithecoid ancestors.

Unfortunately no fossils have yet been found that show the relationship between the catarrhine and the platyrrhine monkeys; but here the precipitin reaction is useful, showing a close relationship between these two groups of monkeys, whose common ancestral stock must date back to the eocene (possibly 50 million years ago).

Fossil tarsioids and lemuroids have told a similar tale of the relationship of the higher primates to the lemurs, with Tarsius as the link. An outstanding example of such evidence is the precocious development of the temporal lobe in the lemurs. The lemurs in turn are shown by the fossil record to be descended from tree-shrews, in which important later characters of primates are present in an incipient form. As Sir Wilfrid Le Gros Clark says: "We may now picture the foundations of the Primates as being laid down at the very beginning of the Tertiary epoch (or more probably in the latter part of the preceding Cretaceous period) . . ."

PSYCHIATRY AND THE COMMUNITY

"SOCIAL PSYCHIATRY" is a subject with a future; for environment affects the clinical features of even the most clearly genetic forms of mental illness, and in the neuroses and in psychopathy its influence may well be paramount. But, like so many promising ventures, social psychiatry faces present difficulties. One is that this term is used in so many different ways. It may mean group treatment, new methods in mental hospitals, or any therapy, prophylaxis, or research related to unusual behaviour, including crime —in fact almost everything except individual psychotherapeutic or physical treatments. Another difficulty is communication. Sociopsychiatric literature is not easy to read, for jargon is too readily substituted for clear thinking. On both these counts a report [1] by a World Health Organisation expert committee on mental health is welcome.

The committee offer as their definition of social psychiatry: ". . . the preventive and curative measures which are directed towards the fitting of the individual for a satisfactory and useful life in terms of his own social environment". They refute the idea that social and "depth" psychiatry are antipathetic. Each illumines the other, and social factors are most significant in patients most accessible to psychotherapy. Cross-cultural differences are rightly stressed. For example, in unchanged agrarian communities, where the mentally sick person is normally accepted, grossly disturbed behaviour is less likely. Again the mentally dull are more readily accepted in communities where literacy is the exception. In these less developed communities specialised treatment is not usually available, but in Nigeria a form of domiciliary treatment is being evolved (similar to that practised at Gheel), which conserves the ties of kinship and avoids exile to the much-feared hospital.

The increasing exclusion of the mentally ill has been common to all rapidly developing societies over the past century and a half, but the committee apparently believe that the trend is now changing. If it is to be successfully reversed, the community must be helped to realise that its interests and safety are not being sacrificed to those of the patient. The traditional attitude of the community to the mentally ill is all-important, and the committee describe the many different forms it can take. Thus, though the primitive belief that mental disorder is caused by demoniac possession is still widespread in some areas and has probably not been entirely superseded anywhere, the idea that insanity is an illness and needs treatment has existed for centuries—for example, among Buddhist monks. In some communities where demoniac possession is firmly accepted it is the devil, not the patient, that is hated; and once the devil is driven out the patient is fully accepted back into the community. By contrast, elsewhere theories of heredity lead to the rejection of a patient, who is not allowed to marry, bear children, or inherit goods. Where mental disease is believed to have a "somatic" or "nervous" origin the attitude is better, and in Nigeria the *babalawo* in treating physical and mental disorders makes little distinction between them. Such impartial attention to mental and physical complaints would, the committee suggest, improve the community's attitude to psychiatrists. Thus in Illinois the term "psychiatric physician" is already more acceptable than "psychiatrist".

A few communities go to the other extreme, and in them a member gains prestige because he is receiving psychotherapeutic help. Here neurosis may be equated with intelligence in the public mind, though, if the patient's symptoms make too great a demand on those around him, he is resented and may be termed a psychopath. In changing cultures the attitude of the community towards their old people is often unfavourable, for these are usually less able and willing than the young to adapt themselves to new ways of life. Social rejection is often class-linked, for to children moving up the social system parents may be an embarrassment. Community attitudes to the mentally sick may be expected to soften where there is insurance against the cost of treatment, and the patient is not a drain on the family resources.

In their recommendations for the future, the committee urge the closest coordination, if not integration, of the mental and general health services. Techniques of information and propaganda need study; for films, brochures, and lectures are sometimes misinterpreted. More "attitude" research is needed. The psychiatrist should give part of his time to training workers, both in and out of hospital, who spend much time in close contact with patients and their families. He could with advantage more often be asked for advice on the mental-health aspects of social planning in the community and in industry. Social science might well receive greater emphasis in the training, not only of the psychiatrist, but also of all those in other branches of medicine, education, and the Law. The training of those concerned with the Law should also include psychiatry. Above all the family must be taught that their attitude can be an important part of the patient's treatment, for rejection and overindulgence are equally undesirable. Modern mass media can sometimes be effectively used in health education of this kind, but only, as the committee rightly insists, if they are provided with accurate and unbiased information.

1. Social Psychiatry and Community Attitudes. *Wld Hlth Org. tech. Rep. Ser.* no. 177. Geneva, 1959. Pp. 42. 1*s.* 9*d.* Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. This report is also published in French and Spanish.

Dr. S. J. CAMERON, emeritus professor of midwifery in the University of Glasgow, died on Oct. 29 at the age of 81.

Special Articles

STAPHYLOCOCCAL CROSS-INFECTION IN SURGERY

EFFECTS OF SOME PREVENTIVE MEASURES

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BRISTOL ROYAL INFIRMARY

WE describe here the results of measures to prevent staphylococcal cross-infection in one ward during a 2-year study in three 28-bed male surgical wards and in the operating-theatre. Epidemiological and clinical findings from the control wards and from the control period in the test ward are reported briefly and will be described fully elsewhere. All the staphylococci were coagulase-positive.

Methods

From Feb. 1, 1956, all patients were listed in special books in which staphylococcal infections were recorded. Closed, undrained wounds could be infected only at operation. They were swabbed if they suppurated severely enough to delay healing (" major breakdown "). Open (including drained) wounds could be infected in the theatre or the wards. The theatre was assumed to be responsible when suppuration started deep in the wound, or when the first swab was positive within 3 days of operation and the wound had not been dressed frequently. Open wounds were swabbed every 4 days. To allow for differences in exposure to ward infection, the open-wound infection-rate was calculated by a modification of the method of Clarke et al. (1954) which gave the average percentage of open wounds acquiring staphylococci every 4 days. The nasal-colonisation-rate, calculated similarly, gave the average percentage of patients' noses acquiring staphylococci per week.

TABLE I—INCIDENCE OF STAPHYLOCOCCAL WOUND INFECTION BEFORE EFFECTIVE PRECAUTIONS WERE TAKEN

Type of wound	No.	Infected in theatre		No. infected in wards
		With major breakdown	With minor breakdown or normal appearance	
Closed ..	1764	17 (*0·98*%)	Not recorded	0
Open ..	592	21 (*3·5*%)	20	214 (*36·1*%)
Total ..	2356	38 (*1·6*%)	20	214

Urine and sputum were cultured when necessary. Nurses' noses were swabbed every fortnight. Many cultures were made from blankets, towels, baths, &c., and, by " settle plates ", from air in the wards and theatre.

The bacteriological methods were those described by Alder et al. (1955), except that nasal swabs were not inoculated into salt broth. Most penicillin-resistant staphylococci were phage-typed (Anderson and Williams 1956).

Clinical Effects of Cross-infection

There was much " silent " cross-infection of noses and open wounds, but wounds infected in the wards usually came to little harm. The most serious consequences of cross-infection were the breakdown of wounds from staphylococcal infection originating at operation, and other staphylococcal complications such as pneumonia and urinary infection. Altogether, 77 (3·3%) of 2356 patients had one of these serious consequences, and 4 died (3 from staphylococcal pneumonia and 1 from infection after an operation for coarctation of the aorta).

In the wards.—More than a third of all open wounds became infected by staphylococci (table I), usually with little or no clinical effect. The process was often a colonisation rather than an infection. But discharges from infected open lesions were the most important source of cross-infection.

Most ward infections were caused by a few " epidemic " strains, all of which were resistant to several antibiotics. This finding was similar to that of Shooter et al. (1958). Most epidemic staphylococci belonged to phage-group III (Alder et al. 1955), but there were two important group-I strains—80 and 52/52A/80. The same epidemic strains caused most of the other staphylococcal complications such as pneumonia (table II). They usually predominated on settle plates, and often colonised patients' noses, which then became sources of infection of their own and other patients' wounds.

Staphylococci were probably often transferred from patient to patient by contact with the nurses' hands and uniforms. Prevalent ward strains were often isolated from nurses' hands. But nasal carriage by nurses was rarely responsible for the spread of staphylococci amongst patients in the wards. This was partly because many nurses carried group-I strains, resistant only to penicillin, which sometimes caused furunculosis but rarely infected wounds (Alder et al. 1955, Thompson and Gillespie 1958). Because we were never able to demonstrate the transference of a staphylococcus of any group from a nurse's nose to a patient in her ward, we must conclude that this was comparatively rare. (But in the theatre nurses' nasal staphylococci were probably important, as described below).

In the theatre.—The theatre was ventilated by a plenum system, which was faulty until May, 1957, with the result that some air from the building was sucked into the theatre. Despite this, comparatively few of the multiple-resistant staphylococci prevalent in the wards were isolated on settle-plates in the theatre.

1·6% of all wounds were complicated by major sepsis from staphylococci implanted at operation (table I). The higher incidence in open than in closed wounds may have resulted partly from the greater complexity of some

TABLE II—INCIDENCE OF STAPHYLOCOCCAL INFECTION, OTHER THAN WOUND INFECTION, IN RELATION TO CROSS-INFECTION RATES IN WARDS

—	Wound cross-infection rates	
	High Ward C (Feb. 1, 1956, to Feb. 28, 1957) and wards K and S (Feb. 1, 1956, to March 17, 1958)	*Low* Ward C (March 1, 1957, to March 17, 1958)
No. of operations	2356*	458
Postoperative pneumonia	12	1
Enterocolitis	2	0
Parotitis	1	0
Furunculosis	3	0
Total	18	1

* These included 222 urological operations, of which 21 were followed by staphylococcal urinary infection. (A valid comparison of the incidence of this complication could not be made, as explained in the text.) Altogether, therefore, there were 39 (1·7%) staphylococcal complications other than wound infections.

TABLE III—RATE OF COLONISATION OF PATIENTS' NOSES AND OPEN WOUNDS BY PENICILLIN-RESISTANT STAPHYLOCOCCI: EFFECT OF EXTRA PRECAUTIONS IN WARD C

Ward studied	No extra precautions	Some extra precautions		Full precautions
Ward C (test):	Feb. 1 to Aug. 31, 1956	Without polybactrin Sept. 1 to Dec. 9, 1956	With polybactrin Dec. 10, 1956, to Feb. 28, 1957	March 1, 1957, to March 17, 1958
Nasal-colonisation-rate (per week—see text) ..	32/261 (*12·3%*)	11/148 (*7·4%*)	12/84 (*14·3%*)	16/511 (*3·1%*)
Open-wound infection-rate (per 4 days—see text)	25/127 (*19·7%*)	11/59 (*18·7%*)	10/74 (*13·5%*)	19/470 (*4·0%*)
	No extra precautions			
WardK (control):	Feb. 1 to Aug. 31, 1956	Sept. 1, 1956, to Feb. 28, 1957		March 1 to June 1, 1957
Nasal colonisation-rate	35/248 (*14·1%*)	21/245 (*8·6%*)		17/137 (*12·4%*)
Open-wound infection-rate	32/177 (*18·1%*)	22/136 (*16·2%*)		18/108 (*16·7%*)
Ward S (control):	March 1 to Aug. 31, 1956	Sept. 1, 1956, to Feb. 28, 1957		March 1 to Oct. 24, 1957
Nasal-colonisation-rate	10/123 (*8·1%*)	23/149 (*15·4%*)		28/283 (*9·9%*)
Open-wound infection-rate	13/94 (*13·8%*)	17/169 (*10·1%*)		40/195 (*20·5%*)

operations and partly from the mechanical effect of drainage.

The distribution of phage and antibiotic patterns among staphylococci causing infections in the theatre differed greatly from those in the wards. Of 45 staphylococci isolated from theatre infections, only 15 (33%) were multiple resistant "ward" strains; 14 of these were prevalent in the patients' own wards and may have entered the theatre on their skin or blankets, even though the blankets were removed outside the operating-room. Most patients took baths on the day before operation and might thus have contaminated their skin, since the same baths were used by patients after operation.

Most of the theatre infections, however, were caused by strains which rarely caused infection in the wards; some were sensitive to all antibiotics, others to all except penicillin. Similar strains were often carried by newly admitted patients and by members of the theatre staff, who were probably their principal sources.

Prevention of Cross-infection

Since we did not know what precautions would succeed, we decided first to introduce as many as possible into one ward, and later to evaluate some of them individually. We describe here the precautions applied to ward C and their effect upon infections in that ward and in the theatre. The other wards served as controls.

We omitted some precautions. Patients with infected open lesions could not be isolated; and we did not attempt to alter the "no-touch" technique of dressing wounds, nor to modify the use of antibiotics.

The Precautions and their Effects in the Ward

After a control period of 7 months, several precautions were introduced in ward C during the next 6 months, and thereafter were kept in use throughout the investigation. The first, at the end of August, 1956, was the treatment of nasal carriers and then the disinfection of blankets and pillows.

Nurses and patients found to be nasal carriers of penicillin-resistant staphylococci were treated with neomycin and gramicidin ('Graneodin') or, more successfully, with neomycin and bacitracin ('Neobacrin') (Gillespie and Alder 1957). (In recent work, a water-miscible nasal cream containing neomycin 0·5% and chlorhexidine 0·1% ['Naseptin', I.C.I.] has given better protection than neobacrin against nasal colonisation by staphylococci.)

Although the earlier treatment was moderately successful in suppressing nasal carriage, table III shows that it had no detectable influence on cross-infection of noses or wounds, perhaps because of the relatively long periods which often elapsed before carriers were detected and treated in wards where patients on the average spent less than 2 weeks.

The blankets and pillows used by each patient were disinfected by exposure for 1 hour to warm moist formalin vapour in an autoclave (capacity 50 c.ft.). Loads of up to 50 blankets were treated at a time. Contact with the chamber wall was avoided by the use of a hemicylindrical wire cage on which the blankets were placed loosely. Some were laid on bars fixed transversely in the horizontal diameter of the cage to facilitate penetration. The vapour was at first generated by an improvised method (Gillespie and Alder 1957), but later, a 'Manlove-Alliott' formalin generator was used. The results of the two methods were similar. Sweep-plates from treated blankets usually showed a reduction of about 95% in colony-count, and the blankets were not damaged.

The disinfection of blankets and pillows was followed by a moderate but sustained fall in the settle-plate counts, from an average of 80 colonies per plate per hour on the 126 plates exposed before Sept. 1 to 60 on the 180 plates exposed between then and March 1, 1957. Cross-infection in the ward did not change appreciably, but the disinfection of blankets may have contributed to the reduced incidence of theatre infection in ward-C patients, which started at this time (as described below).

Four more precautions were introduced in November, 1956: crockery and cutlery were disinfected with a quaternary ammonium compound; the nurses used chlorhexidine ('Hibitane') hand-cream after washing their hands; the ward barber's shaving brushes and razors were disinfected after use by immersion for 10 minutes in 70% alcohol; and baths were disinfected from time to time with hypochlorite and detergent (Boycott 1956).

By the middle of December, cross-infection had not appreciably diminished, and it seemed likely that the high staphylococcal load was being maintained by a few patients with infected discharging wounds who stayed for several weeks in the ward. We therefore decided, as the next step, to spray all open and drained wounds with a solution containing neomycin, bacitracin, and polymyxin ('Polybactrin') to protect them, if possible, from colonisation by staphylococci which might then spread to other patients. From Dec. 10, the wounds, and the inner layers of gauze, were sprayed when dressings were changed.

After the introduction of polybactrin, wound cross-infection fell from 18·7 to 13·5% (table III). Although the small difference was not statistically significant, later experience in other wards suggested that the improvement was real.

By February, 1957, it was clear that although there had been some improvement, there was room for much more. Our final precautions were introduced, therefore, between Feb. 10 and 24. These were: the use of a ' New Welbeck ' vacuum-cleaner instead of sweeping brushes; the replacement of all communal towels in the ward and its annexes by paper towels; the use of hexachlorophane soap by patients and staff; the addition of hexachlorophane to the water for baths and blanket baths (Ayliffe et al. 1959), thereby improving the disinfection of the baths and possibly reducing the number of staphylococci carried on the skin, the importance of which has been shown by Hare and Ridley (1958); and lastly, a regime for nasal prophylaxis.

Almost immediately the rates of nasal colonisation and of wound infection by penicillin-resistant staphylococci fell to about a quarter of their previous values. Cross-infection was undiminished in the other wards, where no extra precautions were taken (table III). There was no compensatory increase in cross-infection by penicillin-sensitive staphylococci in ward C. It appeared that the earlier precautions, supplemented by the final measures, had been successful, and that nasal prophylaxis was probably the most important of the final measures. That it was not entirely responsible for the improvement was shown by an investigation begun in wards K and S in June and October, 1957, which we hope to describe later.

Nasal prophylaxis was achieved by the application, twice daily, of neobacrin ointment to the anterior nares of all patients (but not nurses) from the day of admission. It was much easier to prevent the nasal carriage of " hospital " staphylococci than to suppress it once it had developed. Most patients were able to apply the ointment themselves, using a fingertip, but it was essential for a nurse to supervise them, and to apply the ointment, with glass rods or swabs, to the noses of patients who needed help. With organised supervision the twice-daily nasal-prophylaxis rounds were quickly performed, but without it the precaution was readily forgotten. The ointment caused no irritation. Since the introduction of nasal prophylaxis, all staphylococci have been tested for neomycin resistance, but none was found.

The diminution of cross-infection persisted through the year following the introduction of full precautions, except for a temporary interruption in October, 1957, when ward C was closed for 10 days for redecoration. As soon as it was reopened ward S was closed, and among several patients transferred to ward C was a nasal carrier of the 52/52A/80 strain and another whose wound was heavily infected by the same strain, then prevalent in ward S. During the next 6 weeks this staphylococcus spread to 3 more wounds, and was isolated from dust and from a bath in ward C. It then disappeared, and the infection-rate fell to its previous low level.

The improvement in ward C can be appreciated by comparing the proportion of open wounds which became infected during the 1st and 2nd years of the investigation. From Feb. 1, 1956, to Feb. 24, 1957, there were 95 open wounds, of which 40 (42%) became infected by penicillin-resistant staphylococci, and 4 (4·2%) by sensitive staphylococci. From then until March 17, 1958, there were 108 open wounds, of which only 9 (8·3%) became infected by penicillin-resistant staphylococci, and 5 (4·6%) by sensitive staphylococci.

The reduction of nasal and wound cross-infection in ward C was accompanied by a lowered incidence of other staphylococcal complications, such as pneumonia (table II). This is not surprising, since most complications were caused by strains similar to those which spread among wounds and noses. (Staphylococcal urinary infections, however, were reduced in all wards, largely because of changes in the management of urological patients described by Miller et al. 1958.)

Ward Precautions and Infection in the Theatre

This part of the investigation was complicated by improvements in the theatre ventilating system in May, 1957, when bigger fans were fitted and the sterilisers were modified to reduce the escape of hot air through the extractor ducts which removed steam. Thereafter air flowed from the theatre to lobby, and not in the other direction as before. The bacterial contamination of the air was thus reduced. In the 7 months before the ventilation was improved, 223 settle-plates were exposed, mostly during operations, giving an average total count of 39·5 colonies per plate per hour, with 14·8% of the plates containing *Staphylococcus aureus*. From then until March, 1958, 440 plates were exposed, with an average hourly count of 27·9 colonies, and only 4·1% of the plates contained *Staph. aureus*.

Aerial contamination undoubtedly plays a part in the infection of wounds at operation.

Shooter et al. (1956) reduced the incidence of wound sepsis following a reduction of the bacterial content of the air by the use of positive-pressure ventilation in their theatre. On the other hand, Kinmonth et al. (1958) reported no decline in postoperative sepsis comparable with the fall in the bacterial content of the air when they introduced a cross-draught of fresh-filtered air over the operating table.

The moderate reduction of aerial contamination in our theatre suite had no appreciable effect on the incidence of infection among patients from the control wards K and S; and the reduction of the staphylococcal " load ", when precautions were taken in ward C, was followed by a diminution in theatre infection among patients of that ward alone (table IV). The improvement seemed to start with the disinfection of blankets, which is consistent with the widely held belief that contamination of the patient's skin by bacteria-laden blankets and baths is an important means of conveying staphylococci to the theatre. It was not surprising that a reduction in the ward load of staphylococci brought about a decline in theatre infection, since about a third of the theatre infections were caused by staphylococci prevalent in the wards.

TABLE IV—EFFECT OF PRECAUTIONS IN THEATRE AND WARD ON THE INCIDENCE OF STAPHYLOCOCCAL WOUND INFECTION ORIGINATING IN THE THEATRE

—	Feb. 1 to Aug. 31, 1956: No extra precautions in theatre	Sept. 1, 1956, to Feb. 28, 1957: No extra precautions in theatre	March 1, 1957, to March 17, 1958: Improved ventilation after May 31, 1957
Ward K (control):			
Extra precautions in ward	None	None	Nasal prophylaxis only (after May 31, 1957)
Operations ..	247	233	458
Theatre infections	3 (*1·2%*)	9 (*3·9%*)	12 (*2·6%*)
Ward S (control):			
Extra precautions in ward	None	None	Nasal prophylaxis only (after Oct. 24, 1957)
Operations ..	241	214	451
Theatre infections	4 (*1·7%*)	8 (*3·7%*)	11 (*2·4%*)
Ward C (test):			
Extra precautions in ward	None	Some (see text)	Full precautions (see text)
Operations ..	285	227	458
Theatre infections	8 (*2·8%*)	3 (*1·3%*)	2 (*0·43%*)

Staphylococci on the hands of surgeons may cause wound infection if their gloves are punctured (Devenish and Miles 1939), but this did not seem to be an important cause of sepsis during our investigation. Swabs were taken from 59 gloves worn by surgeons or their assistants, but only 1, from a student, yielded *Staph. aureus*.

Discussion

Staphylococcal cross-infection was very common in the wards, though often clinically latent and detectable only by bacteriological study. Nearly 40% of open wounds became infected by staphylococci in the wards, but few were harmed. The cross-infection was important chiefly because of two consequences, one or other of which affected 3·3% of the patients. These were staphylococcal complications other than wound infection (e.g., pneumonia, urinary infection, enterocolitis, furunculosis, or parotitis) and wound sepsis originating at operation. (Other staphylococcal infections in the theatre were caused by strains which probably came from carriers among patients and staff.)

Staphylococci from the wards probably entered the theatre in more than one way. Contaminated air drawn in from the wards may have contributed until the ventilation was overhauled. The installation of an up-to-date ventilation plant would probably have had more effect on aerial contamination, but the moderate improvement from overhauling the existing plant did not lower the incidence of theatre infection appreciably. On the other hand, the reduction of cross-infection in one ward which followed the precautions taken there was accompanied by a lowered incidence of theatre infection among patients from that ward. Thus our results suggest that the risk of theatre infection is reduced by taking precautions in the wards as well as in the theatre.

While the best methods of controlling cross-infection in surgical wards will differ according to circumstances, there are some principles which probably apply to all. Staphylococci multiply in the infected open lesions and carrier sites of patients, and (less important in our wards), in carriers among the staff. The open lesions are probably most important. Staphylococci are transferred from these sources by indirect contact and by aerial dissemination. Some routes are difficult to control; others can be controlled by disinfecting articles such as blankets and baths. But unless something is done to reduce the multiplication of staphylococci or to remove their sources from the ward, precautions directed against vehicles of spread are likely to be disappointing. Although conditions in maternity hospitals differ from those in surgical wards, the striking reduction of staphylococcal cross-infection which followed the prophylactic disinfection of infants' carrier sites in one nursery stresses the importance of controlling the multiplication of staphylococci at their source (Gillespie et al. 1958).

Our aim so far has been to determine the effect of combinations of precautions on staphylococcal cross-infection, rather than to formulate a system of control. We had to omit some precautions, such as the isolation of patients with open infections; others which we took may have been unnecessary. Nevertheless all our measures, when used together for a year, reduced very considerably the staphylococcal cross-infection. It is important to determine which precautions were chiefly responsible; all that can yet be said is that no one precaution is sufficient by itself. But failure of a single precaution to influence cross-infection appreciably does not invalidate it. We believe in the disinfection of bedding despite its apparent lack of effect in our surgical wards and maternity-hospital nurseries (Gillespie et al. 1958). The pattern of cross-infection in surgical wards is complex. The influence of one precaution may be hidden by the spread of staphylococci from sources or routes unaffected by it. The value of some measures will vary between one ward and another; if, for example, there are many urological patients, preventing the multiplication of staphylococci and other pathogens in their urine is important (McLeod 1958, Miller et al. 1958).

We would stress that no precautions can succeed unless they are applied thoroughly and with an intelligent understanding of their purpose. Our study has necessitated frequent visits to the wards, and it has been easy to keep the nurses interested in the progress of the work. But if similar precautions were to be used routinely, very great care would have to be taken to see that all members of the staff appreciated their importance and their purpose. Otherwise the precautions would probably be forgotten, or applied half-heartedly, especially when staphylococci were causing little apparent harm. The enthusiastic cooperation of the ward-sister and her staff is essential for the success of any scheme for controlling cross-infection.

Summary

Staphylococcal cross-infection was studied in three male surgical wards for 2 years.

Several precautions were applied together in one ward for more than a year—namely, a regime of nasal prophylaxis for all patients; disinfection of blankets and pillows; disinfection of crockery and cutlery; the use of chlorhexidine ('Hibitane') hand-cream by the nurses; disinfection of the ward barber's shaving brushes and razors; disinfection of the baths; the spraying of all open and drained wounds with a solution containing neomycin, bacitracin, and polymyxin ('Polybactrin'); the use of a vacuum cleaner instead of sweeping brushes; the replacement of communal towels in the ward by paper towels; and the addition of hexachlorophane to the water for baths and blanket-baths. The result was that staphylococcal cross-infection in the ward and theatre infections in patients from the ward were reduced.

We thank our Board of Governors for a grant which enabled us to do this work; the surgeons who allowed us to study their patients; Prof. R. Milnes Walker and Dr. K. G. Green for their interest and advice; Mrs. S. M. Baber, Miss O. M. Leigh, Sister M. I. Delahay, Sister M. A. Mellings, Sister D. Pile, Sister K. M. Thomas, and the nurses for their assistance; and Messrs. Calmic for supplying the 'Polybactrin'.

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Symposia

STEROIDS

A SYMPOSIUM on steroid hormones was held by the Empire Rheumatism Council in London on October 23.

Biological Properties

Dr. C. L. COPE (Hammersmith Hospital) said that the physiological properties of cortisone and its analogues could be divided into two separate groups: (1) the cortisol effects (anti-inflammatory, glycogenic, and osteoporotic); and (2) the deoxycortone-acetate-like effects (sodium retention and potassium loss). Dr. Cope did not consider that there was a specific antirheumatic action. The individual cortisol effects could not be separated. In rheumatoid arthritis there was no evidence of subnormal production nor of abnormal turnover or protein binding of hydrocortisone, and no abnormal steroids had been demonstrated. Different properties of analogues were due to variations in potency, ratio of deoxycortone-acetate/cortisol effects, and toxicity.

Relative Merits

Dr. F. DUDLEY HART (Westminster Hospital) said that the dramatic effects obtained in the first few years of cortisone therapy had really been due to overdosage, and relative advantages of newer analogues were probably due more to different dose levels used than to anything else. In small clinical trials on rheumatoid-arthritis patients, using what were considered to be equivalent doses of various analogues, it was found that a majority of patients showed improvement on switching from cortisone to prednisolone, but that no difference could be demonstrated between prednisolone, triamcinolone, and dexamethasone. Dexamethasone might be less diabetogenic than other steroids, and triamcinolone was less likely than other steroids to cause fluid retention but could produce myopathy. Gastrointestinal and other side-effects appeared to be the same with all analogues. Notable individual preferences for one particular steroid were, however, found.

In subsequent discussion it was pointed out that while there was no strong evidence of splitting of cortisol effects in man, antiinflammatory and glycogenic actions had been separated in animals. The state of present assay methods for testing analogues was unsatisfactory; and a method of testing immunological rather than foreign-body-reaction properties was needed. Meanwhile there remained the rather frightening prospect of clinical trials lasting one or two years, to test every new analogue.

Prof. J. R. SQUIRE (Birmingham) mentioned the use of cortisone and prednisone in nephrosis, and considered that there was little difference in side-effects except an increased incidence of gastrointestinal complications with prednisone. He had found no adaptation or decrease in sensitivity to steroids in long-term treatment, and did not believe that the body became tolerant to steroids. Other speakers referred to the need for further research into adaptation: why, for instance, should the initial changes in sodium and water balance induced by cortisone later disappear? The tolerance of very ill patients to steroids was also commented on.

Side-effects

Dr. OSWALD SAVAGE (Middlesex Hospital) had analysed the incidence of complications in 910 cases of rheumatoid arthritis in adults on long-term steroids, collected from eight centres. All the centres had submitted similar numbers of steroid-treated cases, with a remarkably uniform incidence of complications. Apart from facial mooning, the most common complication was dyspepsia, occurring in 32% of cases and probably due to the local effect of the steroid upon the gastric mucosa, since it was less common on treatment with injected prednisolone or corticotrophin. 7% of cases had peptic ulceration; and 5% underwent hæmorrhage or perforation of an ulcer, showing that most ulcers gave trouble. Hypertension occurred in 13·5%, and was not usually severe. No figures were available for osteoporosis because of difficulties in diagnostic criteria, but fractures or vertebral collapse occurred in 3%. Other complications were infections (5·5%), arteritis and peripheral neuritis (4%), mental changes (3%), and abnormal bruising (3%). Apart from dyspepsia all the other side-effects were possibly the direct result of an excess of steroid in the body, and Dr. Savage considered the possibility of chemical tests to detect an excess of steroids before side-effects became obvious.

Prof. E. G. L. BYWATERS (Canadian Red Cross Memorial Hospital, Taplow) stressed that the important consideration in steroid treatment was the ratio of therapeutic efficiency to toxicity. He listed the special features of peptic ulcers developing during steroid therapy. Of the possible factors in their production, gastric acidity was only slightly increased, if at all, by steroids, and ulcers could occur with achlorhydria. Local high concentration in the stomach might be a factor, though ulcers did develop sometimes with parenteral hydrocortisone or corticotrophin. Perhaps concurrent aspirin treatment was partly responsible; and Professor Bywaters cited recent work showing a high incidence of gastrointestinal bleeding with salicylate therapy, but no bleeding on oral steroids unless aspirin were added. Osteoporosis and fractures were complications inseparable from the antianabolic action of cortisol. There was no evidence of the value of anabolic steroids, though calcium loss was diminished by stilbœstrol. Arteritis was known to occur in rheumatoid arthritis in the absence of hormone treatment, but was usually seen in severe, nodular, seropositive forms of the disease, which would tend to be treated with steroids. It was, however, possible that steroids increased the incidence or severity of arteritis.

Dr. PETER DAVIES (West London Hospital) spoke about assessing the risk of complications in an individual case, and said that side-effects in patients on oral cortisone were related to a high level of urinary 17-hydroxycorticosteroids. Members of the symposium differed in their opinions as to whether gastrointestinal catastrophies were usually unheralded or were preceded by dyspepsia. Dr. BARBARA ANSELL (Taplow) said that in 69 cases of Still's disease only 3 instances of dyspepsia had been found, with no peptic ulcers; and Prof. R. E. TUNBRIDGE (Leeds) suggested that the higher susceptibility of older people to peptic ulceration in general would be reflected in the age incidence of ulceration in steroid-treated cases. The same thing would apply to hypertension. Prof. S. J. HARTFALL (Leeds) reported that gastroscopy had shown local inflammation in only 1 of 7 cases following the ingestion of powdered prednisolone. Dr. J. J. R. DUTHIE (Northern General Hospital, Edinburgh) pointed out how the incidence of peptic ulcer rose with increasing dosage of prednisolone and suggested a maximum daily dosage of 10 mg., which met with general agreement. Prof. SQUIRE speculated on the importance of diet as a factor in ulceration and osteoporosis, and thought that this should be considered in controlled trials. Several speakers confirmed the possible dangers of supplementing steroids with salicylates and Dr. A. ST. J. DIXON (Hammersmith Hospital) said that they had found a higher incidence of gastrointestinal bleeding with a combination of aspirin and steroids than with aspirin alone. Dr. SAVAGE remarked that dyspepsia, which was such a problem in the steroid treatment of rheumatoid arthritis, did not appear to be so with asthma or ulcerative colitis.

Dr. H. F. WEST (Rheumatism Department, Sheffield) opened a discussion on the methods of avoiding and combating side-effects. By estimating urinary cortisol and 17-hydroxycorticosteroids with various dosages of steroids, he had shown that daily doses of up to about 30 mg. of cortisol produced only a slight rise in the concentration of hormone available to the tissues. As the dose was increased, however, the concentration of available hormone rose steeply, and side-effects increased proportionately. Apart from instructing patients to take their steroid tablets crushed with food, there were two ways of combating gastrointestinal complications by avoiding a local effect on the stomach. The first was by the use of enteric-coated prednisolone tablets, and the second was to give injec-

tions of corticotrophin or intramuscular prednisolone. In 4 patients with osteoporosis on long-term steroid treatment, Dr. West had found a significant fall in calcium excretion after 6 months on 17-ethyl 19-nortestosterone (' Nilevar ') compared with two control cases. In these 4 patients there had also been an increase in creatinine output, the significance of which was uncertain since there had been no change in muscle mass. Adrenal suppression followed adrenocorticosteroid therapy; and preliminary work had suggested that to anticipate the appearance of adrenocortical inadequacy during hormone withdrawal, estimation of urinary 17-hydroxycorticosteroids, as withdrawal was proceeding, might be of value in determining when further dose reductions could be made.

Dr. COPE stressed the value of urinary cortisol estimation, its presence being strong evidence of a functioning adrenal, and vice versa. Dr. IAN BUSH (Radcliffe Infirmary, Oxford) said that the Norymberski reaction converted a large group of metabolites to 17-ketosteroids, easily measured by standard methods. The difficulty lay in the interpretation of results, in that the total colour reaction of the resulting mixture varied very considerably with the relative contribution of individual steroids in the mixture. In general, this would result in rather lower values being obtained at higher rates of excretion.

Laboratory Work

Prof. C. H. GRAY (King's College Hospital, London) said that it was disappointing that laboratory work on steroids had proved to be of so little help in relation to the casual mechanism of rheumatoid arthritis, or to the clinical control of steroid therapy. Difficulties arose from the multiplicity of adrenal hormones, differing ratios of free and conjugated hormones in the blood, and different ways and rates of tissue metabolism. For adequate assessment of adrenal cortical function, some kind of estimation in both blood and urine was necessary. Professor Gray discussed the estimation of urinary 17-ketosteroids, glucocorticoids, and the Norymberski estimation of 17-ketogenic steroids. The use of radioactive steroids would produce valuable information.

Dr. A. E. KELLIE (Middlesex Hospital) agreed that with the Norymberski technique there was a 50% recovery only, whereas with radioactive cortisol almost 100% was recovered in the urine. More attention should be given to free cortisol in the blood. Dr. WEST said that 17-hydroxycorticosteroids rose during the last three months of pregnancy, correlating with clinical remission of rheumatoid arthritis, but Dr. I. H. MILLS (St. Thomas's Hospital, London) said that, while a rise in plasma-hydrocortisone had been observed during œstrogen administration or pregnancy, there was not much information as to what happened to the important ultrafiltrable fraction. It was conceivable that pregnancy remission had nothing to do with steroids.

General Discussion

Dr. A. G. S. HILL (Stoke Mandeville Hospital, Aylesbury) had found a single nightly dose of 5 mg. prednisolone useful in improving morning stiffness. Purpura and dyspepsia were the only common side-effects. With regard to purpura, Dr. DUTHIE commented on the paradox that capillary resistance, low in rheumatoid arthritis, was raised by steroids, which nevertheless appeared to cause bruising. Other speakers remarked that there was a difference between normal and steroid bruising, which was more like senile purpura.

Dr. DUDLEY HART spoke on the steroid withdrawal syndrome and neuropathy. Of 35 cases of rheumatoid arthritis and neuropathy, 27 had been on long-term prednisolone. In 4 of these florid neuropathy developed two weeks after steroid withdrawal—in some others after conversion from one steroid to another. The neuropathy was characterised by being mainly sensory, symmetrical and involving the feet more than the hands. It occurred in severe cases and the prognosis appeared to be poor.

Dr. GEORGE FEARNLEY (Royal Infirmary, Gloucester) discussed the indications for steroid therapy in rheumatoid arthritis, which he thought were economic necessity, a downhill course, as a temporary expedient for orthapædic measures, or with complicating amyloid nephrosis. Dr. DUTHIE also enumerated various factors indicating prognosis and hence the suitability for steroid treatment. The type of case most meriting steroids was a woman of under 50, not crippled, with disease of insidious onset, a positive Rose-Waaler test, and erosions, and not responsing to conservative treatment.

Sir CHARLES DODDS, the chairman, drew attention to the confusion being caused among general practitioners by commercial representatives and literature, particularly with regard to new steroid preparations and their alleged lack of side-effects. Among suggestions put forward was that there should be a schedule for steroids similar to that for barbiturates. Dr. BUSH, however, pointed out that much harm would be avoided if early investigations were performed and reported in a critical manner.

POLAR MEDICINE

A SYMPOSIUM on this subject was held at the National Institute for Medical Research, London, on Sept. 18.

Dr. H. E. LEWIS (British North Greenland Expedition, 1952–54) reviewed the recent history of British physiological research in polar regions. The organisation of the work had become centralised under the wing of the Division of Human Physiology of the National Institute for Medical Research. Much of the earlier work had been fragmentary, not because of lack of skill but rather, perhaps, because of lack of a central theme running through it. With a continuing programme of observations, numerous polar legends had been examined and put to the test.

Dr. J. P. MASTERTON (British North Greenland Expedition, 1952–54) gave an account of how a number of casual observations and well-known facts had led to some well-instrumented experiments into energy expenditure and food intake in cold regions. From the fact that men in the cold have a high fat intake and that huskies eat human fæces, experiments and further observation led to a number of conclusions: that, in spite of fat intakes of almost 300 g. per day, men absorbed virtually all of it, leaving the coprophagic huskies no nutritional value; that men expended very large amounts of energy (4500–5000 calories per day) while travelling with dog-sledges; and at their base camp, with routine duties, energy expenditure of the order of 3900 calories per day was usual.

Dr. A. ROGERS (Trans-Antarctic Expedition, 1957–58) continued this work. Measurements made with the integrating pneumotachograph confirmed earlier estimations of the very high energy output of men at base.

Major J. M. ADAM, who took part in the Anglo-American Physiological Expedition of 1958, suggested, from measurements made on men of the T.A.E. during the last few days of the trans-continental journey, that, although travel with vehicles was obviously less strenuous, the daily energy output actually approached that of sledging because of the longer day.

Dr. L. G. C. PUGH described experiments performed in the Antarctic with the Anglo-American Physiological Expedition to measure effects of solar radiation on man. He found that, despite the low altitude of the sun, men travelling during the summer could gain more than 300 calories per sq. m. per hour, which would be the same as raising the ambient temperature by 10°C. The gain under desert conditions was of the order of only 240 calories per sq. m. per hour.

Dr. H. T. WYATT (Falkland Islands Dependencies Survey) described the persistence of cold diuresis throughout a year's stay in the Antarctic, and also described trials of a new dog ration.

Dr. J. GRAHAM (F.I.D.S.), following up observations made on the British North Greenland and Trans-Antarctic Expeditions on sleep rhythm, showed that even in this remote area of the world social pressure partially determined the length of nightly sleep—i.e., about 8 hours in 24—and that when some of this pressure was released by the departure of the base leader the average nightly sleep went up to above 9 hours. He could find no clear correlation between length of sleep and the previous day's work.

Sir VIVIAN FUCHS, scientific director of F.I.D.S., admitted, on seeing the size of the meeting, that " physiology has come to stay in the Antarctic," but pointed out that up till now it had naturally received a rather low priority. He stressed the well-known difficulty of persuading subjects to cooperate in what might sometimes be rather unpleasant experiments. The suggestion that for better results it would be advisable to have two medical men at one station was obviously sound. The meeting was heartened by his suggestion that a physiological station in the Antarctic might be feasible. Many problems of cold-climate physiology could be investigated at such a station, which might indeed be as useful in this field as the early high-altitude expeditions in the Andes were to respiration physiology.

Sir RAYMOND PRIESTLEY, a veteran of polar exploration, suggested that since his day the psychological problems had changed considerably; where there was once complete isolation and real hardship there were now radio and relative comfort; but there was still the problem of living in constant close contact with one another. There was much to be learnt from intelligent, discreet observation.

The discussion touched on other topics for investigation; for example, it was felt that the time had come to observe the reaction of women as well as of men to polar conditions, and that investigation into the adaptation of the local fauna would be of considerable value.

Public Health

Monitoring of Radioactive Fallout

IN a memorandum [1] summarising Government action on radioactivity, recently sent to local authorities and to their medical officers of health, one of the subjects is the monitoring of fallout. In 1957 the Prime Minister approved revised arrangements under which the Agricultural Research Council was responsible for monitoring soil, herbage, farm animals, and milk and other foods, and the Medical Research Council for measurements of radioactivity in human bone. The Atomic Energy Authority retained responsibility for the analysis of radioactivity in air and rain water, and the Authority, in conjunction with the Ministry of Housing and Local Government, also measured the activity in selected sources of drinking water. A joint committee of the Agricultural and Medical Research Councils and the Development Commission supervises the monitoring programme, and has, for that purpose, set up a special subcommittee, under the chairmanship of Dr. J. F. Loutit. Countrywide and local surveys now being undertaken involve the annual collection of several thousand samples of milk, water, green vegetables, potatoes, and flour.

In a letter to medical officers of health, Sir John Charles, chief medical officer to the Ministry of Health, says it is largely because of the extent of these arrangements that the Ministers concerned have said that they see little advantage in widespread monitoring by local authorities. Sir John continues:

" It has sometimes been argued that, whatever the Government may be doing to watch the national situation, local authorities have a duty to their residents to make sure there is no local hazard. I doubt if this is a truly valid distinction, at any rate in relation to fall-out. Such levels of contamination as there is reason to think exist are too low to be detected except by complicated apparatus and highly refined analysis, and the level in any one sample is in most cases very small in comparison with the comparable radioactivity from elements naturally present in the sample. The standards by which levels of radioactivity from fall-out are judged are those which have been recommended by national and international research organisations as acceptable for continuous consumption over a whole lifetime of seventy years. A level at which it would seem desirable to withdraw a product from consumption over a short term would be so many thousands of times higher that, so long as the present low average levels persist, there can hardly be presumed to exist the possibility of local contamination of food within the meaning of the Food and Drugs Act, such as might justify local monitoring on this account."

1. Ministry of Housing and Local Government circular no. 57/59.

In England Now

A Running Commentary by Peripatetic Correspondents

THE Motor Show drew half a million people, or so I hear. Judging from my terrible experiences there last week this may be an underestimate; I saw them all, and, as a result, very few motors. Here's one motorist that won't help to make the 1960 show the greatest ever. When I want to look at cars it will be at one of those splendid showrooms round Piccadilly which always seem completely empty.

But there seems little doubt that the motorcar has come to stay. My father and mother always had the greatest doubts about these new monsters, and as late as the mid-'thirties I recall that the annual journey of 30 miles to London for the Christmas shopping needed weeks of careful planning. Sandwiches were cut, maps were studied, and the vehicle was carefully overhauled by the young man in my father's hospital who was held to " understand " cars. On the appointed day we ground tremulously away, the young man at the wheel, expecting disaster at every turn. The cantankerousness of our machinery justified our forebodings, and we were plagued with punctures, kicking starting-handles, boilings-over, and the like, though no crashes of course—we went far too slowly. The rare longer journey undertaken courageously by my older brother was the occasion for even more feverish planning, in particular the preparation of food by my mother—consciously lest the dread machinery strand them for days on some lonely moor, but unconsciously doubtless as a propitiatory rite to the Gods of Motoring.

As the youngest son, rebelliousness was inevitable and I duly drove much too fast and had three fair-sized crashes, once turning the car right over, and thus broke even with an insurance company that had been doing very nicely out of us. The years have passed and my no-claim bonus is at the summit: I am allegedly the safest of all risks in early middle-age with a family saloon and children (foolish to say this). As I watch my neighbours bumping off themselves and others with motor-cycles, there is no doubt whatever that my parents were right: motoring *is* a fearsome business, and the sooner we all realise it the better.

* * *

The sudden snap of wintry weather made me put on my new suit. My others have grown small for me, but this new suit (of unusual colour and design) gives plenty of room for those extra articles of clothing which make all the difference between starvation and comfort on a cold day.

At breakfast my family approved the suit. At the office our head typist said, " Clothes do make such a difference." The caretaker said I was " perjink ". The health visitor thought that the line was lovely and the pattern not in the least loud. Others took it in at a silent glance. I paid no attention to a remark by the health inspector about Joseph's coat, as I am sure it had nothing to do with me.

I have always given names to my suits. There was my Final-year Suit, my Qualifying Suit, my Darlington Memorial Suit (bought in my first house-job): then my Marriage Suit, and my Demob Suit. I still have two Anæsthetic Suits (the ones that have grown small) bought with the fees from dental anæsthetics. My present Sunday suit is known as my Polio Jags Suit, as I was able to buy it after doing extra inoculation sessions for another authority. When I met my chief he eyed my new rig-out and said, " Oh, Boy, what a suit! " I told him about my suit-naming custom, and he at once christened this one my Tycoon Suit. " It was the only one in the shop that fitted me," I said defensively, " 44 Portly, is how the assistant there described it."

* * *

It was a pity that it rained in Vienna when our non-peripatetic colleagues were basking in the warmth of an anomalous English summer. Fortunately no amount of nasty weather could dim the many facets of this splendid city and even if the Danube flowed grey, the gilt had not been washed off the baroque. Our party of dermatologists were made very welcome

at a reception given by the Burgermeister in one of the halls of the Rathaus. Both here, and at a less formal party in one of the beer cellars, we learned the strength of Austrian hospitality. Vienna means something slightly different to every traveller, and is at once the home of the Hapsburgs, the inspiration of Strauss, and the setting of *The Third Man*. To us it was the city where Hebra built a clinic which has influenced the whole course of dermatology.

From Vienna to Zagreb where Professor Kogoi's clinic is one of the most up to date in Europe. If it is a long way to Yugoslavia, our hosts never let it feel so. Brilliant organisation provided three days of constant interest and we saw not only a first-class dermatological clinic, but some excellent modern hospitals and an industrial research institute which is unique of its kind. We met administrators who answered our questions with patience and frankness, and wherever we went found the people exceptionally friendly.

For our part, we were foresighted in choosing a president who could make impromptu speeches in fluent German, and an interpreter who translated with ease from English into German, German into English, and once (after a good lunch) English back into English.

Lastly, a tribute to the unknown Yugoslav whom we called Tarzan from the wealth of muscle which showed when he stripped to the buff. We met this character in the dead of night after our car had broken down. He spent the remaining hours of darkness patiently trying to coax our petrol-pump back into life and at dawn he succeeded. We celebrated with Slivovitz as the sun rose.

* * *

I suppose it is uncharitable of me to ostracise all the little Guy Fawkes rackets that abound in my part of Lambeth, but this year scarce a doorway or bus stop is unadorned by a couple of sacks stuffed with straw or unsurrounded by hordes of brats claiming pennies for the guy. My conscience is cleared somewhat by a steadfast refusal to allow my own lot to take one of my old suits or to supplement their pocket-money, though at times this does no more than make me feel mean both ways. Inferiority feelings over this parsimony were finally stilled, however, when I spotted, across the road from my room, one of these teams at work. Business was brisk and every ten minutes or so an old man, emerging from the doorway behind, collected the takings and went unsteadily in again. It chanced that on my way home—from Guy's Hospital oddly enough—we coincided. In response to my very dirtiest of looks he remarked plaintively: "Well it's a very good Guy".

* * *

In my Newfoundland practice I travel mostly by boat, and usually, it seems, I travel at night in the rain. When I open the patient's door and stand in the light, blinking and streaming rain water on to the floor, I probably look dramatic enough. But I am nothing compared with what awaits me. My patients live in isolated homesteads, scattered up and down sixty miles of wicked coastline, yet whenever I answer an urgent call I always find what I can only call a "death watch" waiting for me. A dozen or more people sit in the room next to the sick-room, saying not a word, just waiting, rather like crows in a tree. Silently they watch me cross the room; I feel that I should look more purposeful, but the whole business sends shivers up my spine. The one lamp is taken into the sick-room and outside they sit waiting in the dark. I still do not know how the word gets around, and certainly to travel the distances they must cover is a feat of determination. I do know that if ever I fall sick the door of my house is going to be locked; no-one is going to sit waiting outside my room. These folk are so often right.

* * *

She told me she was feeling much worse. I asked what her symptoms were, and found that in one respect at least her chest had improved. "You have no longer any troublesome sputum. Your cough is now dry," I said, hoping to encourage her. She looked at me. "Well, you see, Doctor, it's the dry rot."

Letters to the Editor

CANCER: TO TELL OR NOT TO TELL?

SIR,—I read with interest the letter from Mrs. Cummings (Oct. 24), and regret that I must agree with her that "many doctors unwittingly fail their patients". This is because they do not understand what their patients are thinking, particularly when the patients believe that there is a possibility of cancer. Some doctors argue that if the patients want to know they will ask. This is *not* true and I have ample evidence. Each year I give many lectures on cancer (80 last year) to the public, and during question time on many occasions a member of the audience has stood up and said "you ask us to go to the doctor if certain symptoms occur because of the remote possibility that such symptoms may suggest the start of a cancer, but I could not talk to my doctor about cancer, I hate being laughed at, and in any case he would not tell me the truth".

Many surgeons I fear do not realise that in their wards there are patients who worry lest they have cancer because they have not been told about their illness. Generally this is due to the rush of hospital life, but sometimes due to the fact that the surgeon lives in the past, and believes that the medical profession is a priesthood, and that the consultants are the High Priests and should not be approached or questioned. It should be the duty of someone in every ward to see that the mind of every patient be put at rest by knowing something about their illness.

Two questions arise from your correspondent's letter:

(1) Should a patient be told that death is imminent? My answer to that is *Never*, because generally it is unnecessary, and a patient should never be deprived of hope.

(2) Should a patient be told that he or she is suffering from cancer? There are cases where the value of telling the patient may be in doubt, and in such cases the final decision must rest with the family doctor, in consultation with the relatives. The opinion of the nurse who sees so much of the patient is often of value. In the vast majority of cases the patient should be tactfully told for the following reasons:

(1) In the majority of cases it is not possible to deceive the patient who is dying of cancer. In some cases the patient pretends to be deceived, for the comfort of their relatives and doctor. All patients are not such fools as doctors think.

(2) When the patient does realise it, he believes that the doctor, whom he may have attended for many months, is at fault because he did not diagnose the condition when the patient first became ill.

(3) If the relatives are told, and if in later years one of them thinks he has cancer, it will be difficult for the doctor to convince him otherwise, and he may suffer years of fear and doubt.

(4) Most patients prefer the truth, however unpleasant, rather than be left in doubt.[1]

(5) If the public never hear of a "cured" case, they will consider the disease always incurable, and therefore refrain from seeking advice which they believe cannot help them.

(6) This "hush hush" concerning cancer is undermining the confidence of the public in the medical profession. I know personally of patients who do not trust their doctor in this matter, and in one case the woman believed for three years she had a cancer because of the way in which the doctor answered her inquiries.

Cancer Information Association,
337, Woodstock Road,
Oxford. MALCOLM DONALDSON.

1. Aitken-Swan, J., Easson, E. C. *Brit. med. J.* 1959, i, 779.

REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—Mr. Kenneth Walker seeks to exploit the tragic suicide of a youth of 17 in prison (where he was on remand on a charge of sexually assaulting a boy of 13) in order to get the law on homosexuality changed and in particular to get the recommendations of the Wolfenden Committee adopted. I and many others think that these recommendations themselves have already done considerable harm to the youth of the country and that, if the first recommendation were implemented and one form of homosexuality were legalised, then all forms of homosexuality would be encouraged.

Mr. Walker omits to tell us what one of the newspapers reported—that this was not the first time that this youth had been charged with this offence. I can well imagine that the magistrates or judge in chambers who refused bail may have been confronted with a case in which a youth appeared to be a menace to small boys and was not under effective control at home and had to be kept in custody. I do not know if this was so. Two days ago the newspapers reported that the Home Secretary had asked for the papers of the case, and two days before that Mr. Walker, without telling us what might be the pivotal fact, had dashed into indignant print. Then he does not give us any evidence that the suicide had anything to do with the nature of the charge. Some time ago another youth committed suicide in prison; he was, I think, being charged with robbery with violence. I very much doubt whether his particular offence had much to do with his suicide; it was just a case of a poor lad being in desperate trouble.

Mr. Walker writes: "Whilst the Church has come down courageously and strongly on the side of the Wolfenden Report the medical profession . . ." This is demonstrably untrue: the Church has done nothing of the kind. In the House of Lords debate on the Wolfenden Report (*Hansard*, Dec. 4, 1957) the Archbishop of Canterbury and the Bishop of St. Albans spoke in favour of the homosexual recommendations, the former making the reservation that he thought that sodomy should remain a crime even between consenting adults, while the Bishops of Rochester and Carlisle spoke uncompromisingly and sternly against them. In the Church Assembly 155 voted in favour of this part of the Report, 138 against it, and 407 abstained from voting (*Church Times*, Nov. 27, 1957). The General Assembly of the Church of Scotland "by a great majority endorsed their committee's opposition to the Wolfenden findings on homosexuality" (*Times*, May 27, 1958). So much for "courageously and strongly".

Then I dissent from him in thinking "that no political party regards the matter as an urgent or even an important one". Anyone who listened to the debate in the House of Commons or read it (*Hansard*, Oct. 26, 1958) must have realised that it is not a party matter at all and that almost every speaker sensed the gravity of the subject; that the liberty of the individual was involved, that it might affect generations unborn, that it could bring disgrace and disaster into any home in the country, and that injudicious recommendations might start a spreading contagion that could be hardly stayed.

Homosexual practices can be a corrupting menace to any society and particularly to its youth; these practices are often associated with grim tragedy; and those who condone or encourage them even with the best motives are cruel beyond their knowing.

Beckley, Rye. C. G. LEAROYD.

SIR,—Mr. Kenneth Walker's reproach last week is timely and justified. The law relating to homosexual offences is largely out of touch with modern understanding. As a result things are done in our name that ought to shock the conscience of a civilised country. At Newport Assizes, as lately as 1942, thirteen men were sentenced for homosexual offences to terms of imprisonment ranging from 10 years to 12 months and making a total of 57 years. Last year some 342 persons were imprisoned for offences of this nature. And now there is the suicide of a boy of 17 whilst on remand in custody awaiting his trial.

Whether we like to admit it or not the fact remains that sexual misconduct between adolescent males is remarkably common. And it would be quite wrong to suppose that it mainly occurs in boarding-schools and other institutions where the sexes are segregated. Young people who get into these difficulties need a good deal of help. Many of them then stand a chance of developing normally. To treat them as criminals is to abandon ourselves to irrational impulses, and anyway those of us who work with boys of the age-group most often involved can testify to the failure of the traditional outlook.

Clearly a responsibility falls upon our profession. Public order and decency must be preserved and young people must be protected against exploitation. All agree about this. But the public is not yet able to contemplate a change in our laws without anxiety. We are in a position to influence public opinion and we ought to get on with it.

Godalming, Surrey. J. A. WAYCOTT
Medical Officer to Charterhouse School.

CHOLESTERYL ESTER FATTY ACIDS IN ATHEROMA AND PLASMA

SIR,—On Sept. 28 at a meeting on atherosclerosis in Brussels, Professor Verdonk [1] discussed my hypothesis about the possible role of a relative deficiency of essential fatty acids (E.F.A.) and concluded that it was not supported by the published analyses of atheromatous plaques. In your issue of Oct. 17 Professor Morton and his colleagues add further analyses from which they rightly conclude that "The general picture is confused". Part of the confusion may arise, I believe, from a chemical error that has been made in your columns on various occasions by distinguished fat chemists, and to which I now venture to call attention since it is possible that these analyses may in fact be found to support the hypothesis.

These chemists seem to assume that, when they estimate long-chain fatty acids by the alkali-isomerisation technique or by gas-liquid chromatography, they are able to estimate linoleic acid (*cis*-9:10, *cis*-12:13-octadecadienoic acid). The former method estimates groups of fatty acids of equal degrees of unsaturation from two (dienoic) to six (hexaenoic) double-bonds, whatever the chain-length and position of the double-bonds. The gas-liquid chromatographic technique measures "single components" according to James and his colleagues,[2] but this appears to be open to question since in a later paper [3] they alter "linoleic acid" to "linoleic + linolenic acids".

This is not just an academic question, for a possible reason I have discussed [4] in the presence of Professor Morton and Dr. James. We know from the distinguished work of Klenk, Mead, and others that there are three classes of unsaturated fatty acids. As I have explained in your columns before,[5] the linoleic and linolenic classes of E.F.A. differ in the position of the first double-bond counting from the methyl end, this being in the 3:4 position in linolenic acid and the 6:7 position in

1. Verdonk, G. *Nutr. et Dieta*, 1959, suppl. to vol. **1**, 124.
2. James, A. T., Lovelock, J. E., Webb, J., Trotter, W. R. *Lancet*, 1957, i, 705.
3. James, A. T., Lovelock, J. E. *Brit. med. Bull.* 1958, **14**, 262.
4. Discussion in Proceedings of a Conference arranged by Unilever Ltd., May, 1959; p. 126.
5. Sinclair, H. M. *Lancet*, 1959, i, 474.

linoleic. The third class, which can be readily made in the body from carbohydrate or saturated fatty acids, is the oleic class which has the first double-bond in the 9:10 position.[6] The fatty acids in all three classes can be anabolised in the same way [6]: by introducing an extra double-bond towards the carboxyl end, then two more carbon atoms, then another double-bond, and so on. In this way oleic acid is transformed into a dienoic acid (an isomer of linoleic acid) and then into a C_{20}-trienoic acid, and this accumulates in E.F.A. deficiency in lower animals, perhaps (teleologically) because the animal is deficient in E.F.A. and so makes the only type of polyunsaturated fatty acid that it can readily synthesise. My hypothesis is that in a relative deficiency of E.F.A. other fatty acids may displace the usual ones (E.F.A.) in compounds such as phospholipids and cholesteryl esters; since linoleic acid (C_{18} with two double-bonds) is the predominant fatty acid found normally in cholesteryl esters, it would not be unexpected if oleic acid (C_{18} with one double-bond) and the isomer of linoleic acid formed from it were found in a relative deficiency of E.F.A. In fact, there is an indication that quite large amounts of oleic acid do occur in the cholesteryl esters of atheromatous plaques: Professor Böttcher and his colleagues,[7] who concluded that their " results do not support the hypothesis of Sinclair (1956) and others ", found 35–45% which, with 5–10% palmitoleic, gives a possible 40–55% monoenoic. Tuna and colleagues [8] found 41% monoenoic according to Morton's calculation, Lewis [9] 22%, and Riemenschneider and colleagues [10] 61·5%, which is nearly three times the proportion (23·5%) they found in the cholesteryl esters of plasma from supposedly normal persons. James et al.[2] found more oleic acid in the acetone-soluble lipids (which include cholesteryl esters) of persons who had had a coronary thrombosis than in those of controls. Morton et al. add chaos to their admitted confusion by giving figures for monoenoic acids in tables I and II, and for oleic acid in tables III and IV, without informing us how palmitoleic acid (known to be present in atheromatous plaques) was separated from oleic in the latter tables. These authors appear to have assumed that the dienoic acids estimated by alkali-isomerisation or the peaks that appear in the same position as does linoleic acid in gas-liquid chromatograms represent linoleic acid, and because they think they find considerable amounts of this it is concluded that the E.F.A. hypothesis is wrong. Since an isomer of linoleic acid would be expected in E.F.A. deficiency, their criticism is not conclusive on present evidence. We are attempting to identify the dienoic acid in cholesteryl esters and phospholipids, and also to estimate the E.F.A. content biologically; and we are making plans for a large trial of the incidence of ischæmic heart-disease in middle-aged men on a diet high in E.F.A. as compared with the typical " good " British diet which so often has a relative deficiency. But it is not easy to get the necessary funds despite the heavy and increasing toll of death and disability from this disease.

This distinction between E.F.A. and unsaturated fatty acids that are not E.F.A. is very important in practice. Dr. Berry of the Ministry of Health has recently advised [11] that coronary patients should consume " at least . . . 40 g. of linoleic or other polyunsaturated acid daily "; this is equivalent to about 75 g. of corn oil daily (3 oz.). There are many polyunsaturated fatty acids that are not E.F.A., as in tung oil; I have a sample of this containing 70% of a conjugated isomer of linolenic acid (C_{18} with three double-bonds), with an iodine value of 230; this vegetable-seed oil produces higher values for plasma-cholesterol in rats than are produced by any comparable dietary means,[12] and I challenge Dr. Berry (or other enthusiasts of the unsaturated-fatty-acid heresy such as Dr. Ahrens or Professor Keys) to consume at least 57 g. (2 oz.) of it daily.

Oxford. H. M. SINCLAIR.

6. Mead, J. F., Howton, D. R. *in* Essential Fatty Acids; p. 65, London, 1958.
7. Böttcher, C. J. F., Keppler, J. G., ter Haar Romeny-Wachter, C. C., Boelsma-van Houte, E., van Gent, C. M. *Lancet*, 1958, ii, 1207.
8. Tuna, N., Reckers, L., Frantz, I. D. *J. clin. Invest.* 1958, **37**, 1153.
9. Lewis, B. *Lancet*, 1958, ii, 71.
10. Riemenschneider, R. W., Luddy, F. E., Morris, S. G. *Amer. J. clin. Nutr.* 1958, **6**, 587.
11. Berry, W. T. C. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 118.
12. Hegsted, D. M., Andrus, S. B., Gotsis, A., Portman, O. W. *J. Nutr.* 1957, **63**, 273.

ABSORPTION OF VITAMIN B_{12}

SIR,—Booth and Mollin [1] reported clinical observations which suggest that the major site for the absorption of vitamin B_{12} in man may be the ileum. They noted malabsorption of vitamin B_{12} in several patients with ileal resections, while absorption of the vitamin was normal in a patient subjected to resection of 8 ft. of jejunum.

We have recently observed an elderly man who developed severe steatorrhœa and hypoproteinæmia after a subtotal gastrectomy performed at another hospital. A Schilling test was carried out with ^{60}Co-labelled vitamin B_{12} incubated with neutralised human gastric juice, and 27% of the radioactive dose was excreted in the urine in 48 hours. This result is well within normal limits in our hospital. The patient's debilitated condition prohibited surgical intervention, and at necropsy it was noted that a gastroileostomy had been performed 5 ft. from the ileocæcal valve.

The finding of apparently normal absorption of vitamin B_{12} in a patient in whom all of the small bowel except the terminal 5 ft. of ileum had been effectively bypassed is consistent with the current concept that the distal ileum may be an important site of B_{12} absorption in man.

Research Laboratory,
Veterans Administration Hospital,
Boston, Mass. ROBERT M. DONALDSON.

1. *Lancet*, 1959, i, 18.

NEW WORDS REQUIRED

SIR,—To see last week one letter soliciting a new word to characterise human error, followed by another from that redoubtable iconoclast, Dr. Richard Asher, who proposes Texidor's twinge as a new name (surely preferable to precordial catch which might be taken for a glee, for a common, but hitherto anonymous, feeling) is a combination of circumstances which seems to invite fools to rush in where angels fear to tread. In this spirit, then, and mixing Greek with Latin most unashamedly, I suggest that the pilot who has misread his instruments, or the doctor his patient's disease, should be said to have dysreacted. They may or may not be confirmed dysreactors but even if they are their degree of dysreactivity will no doubt vary from time to time. Their error may be culpable or not but in either case it will constitute a dysreaction. A great advantage of this name is that the opposite conception—of eureactivity—is neat and ready to hand. And what fun it would be to investigate eureactivity among the dyspeptic.

The prefix dys- is preferable to mis- since the latter has just that flavour of mistakenness, even of evil, about it which Mr. Caplan seeks to avoid. The Shorter Oxford Dictionary renders mis- as " bad, wrong, wicked " whereas dys- is said to carry the notion of " hard, bad, unlucky etc.", which suggests an unlooked for fall from grace rather than damnable error.

" The rain it raineth every day " and it is just as wet whether it is described as rain or precipitation. Of course the man who has dysreacted has still made a mistake and whatever new name is made to describe his error its use could be justified only because its emotional frigidity allowed investigators to go about their work calmly and thoughtfully. It would be a pity, though, if the notion arose that the dysreactor was necessarily always blameless,

but I fear that this might happen in the present climate of psychological opinion, and the new name might turn out to be yet another means whereby mankind presumes to avoid man's personal responsibilities.

Aberdeen. ALAN LYELL.

EXTRADURAL HÆMORRHAGE

SIR,—Your annotation of Oct. 17 is a good review of current opinions, and the hints on diagnosis are most timely. But are you right when you conclude that the only way to reduce mortality (having agreed, as we all have done for years, that early diagnosis must come first) is to transfer all suspected cases to a neurosurgical unit?

I believe that the better results of treatment in such units are not entirely due to the special skill and experience brought to bear, important though these attributes are. As in other fields of treatment, a very great deal depends upon the selection of cases. Just as the mortality of burns appears to be less in a plastic unit—because the really bad cases are seldom represented in their true proportion, since not all of them reach the unit—so perhaps it is even more true in the head-injury problem. The slower type of case, with a favourable prognosis after surgical treatment, will inevitably carry a lower mortality than the common rapid, and mixed kind of injury which is still treated in the general hospital.

The emergency treatment of a patient in cerebral compression, with incipient coma and the threat of respiratory arrest, will properly remain the responsibility of the nearest trained general surgeon on the spot. Delay and division of surgical responsibility in this kind of crisis will not reduce the mortality. Deaths in transit may protect the figures of the special unit, but they will not console the family who will readily perceive that a wrong decision has been made.

Early diagnosis, yes. Immediate transfer, no.

London, W.1. H. H. G. EASTCOTT.

LEUKÆMIA AND GEOGRAPHY

SIR,—I was interested in the paper by Dr. Phillips (Oct. 24), in which he analyses leukæmia deaths by geographical counties for the years 1950–57 and advances the hypothesis that radioactive fallout may account for the apparent rise in the incidence in certain Western counties.

Although deaths from leukæmia were not broken down into local-authority districts in the Registrar General's Statistical Review until 1950, neverthless I have the figures supplied by the Registrar General for the three years 1947–49. In the accompanying table I have taken the 8 counties mentioned by Dr. Phillips as showing a significant rise and added the figures for 1947–49 to the details already given.

When considered over the eleven years instead of eight, Westmorland and Brecon show a decreasing rate; the remaining 6 counties still show an increase but, with the exception of Durham and possibly Monmouth, the figures at present appear too small on which to base conclusions.

I have added figures for Cornwall to the table, as Dr. Phillips suggests that Cornwall may be one of the next counties to show effects of radioactive fallout.

Truro, Cornwall. E. R. HARGREAVES
Deputy County Medical Officer.

THE NATURE OF EXPERIENCE

SIR,—I am compelled by Dr. Liversedge (Oct. 17) to ask you for more space. My first letter was directed at a fallacy in the review (Aug. 29) and not at the sense-datum theory which I have only watched from a distant seat in the gallery, but even from there it has been amusing these past few years to see " neurosophists " clinging to the theory when the world of logical and linguistic anatomists have cleanly disposed of it. Dr. Liversedge holds a place on the front bench of this argument: he is a " neurosophist " himself, and the theory is ready-made for " neurosophists "; no wonder they love it, reeking as it is of physiology, neuroanatomy (and physicochemistry).

The theory does not help me to look at pictures, although Dr. Liversedge tells me I have to accept it " in explanation of the complex relationship existing between object, artist, and observer." Is this relationship so complex? Dr. Liversedge is free to use his judgment of good and bad as a first and not a last resort. I have never searched for this " relationship " and would not know how to start. To me he is mixing creation with interpretation and if he whittled these two functions down to physicochemistry or neuroanatomy he might find them radically different.

Here I refer him back to the three classes of " abstract " painting which I claim can be recognised. Two of these are objective in disguise but the " coverage " men to me are truly non-representational. I say they must start from a blank area, or they are objective, and their cerebral efforts are active not sensory. If Dr. Liversedge searches a relationship with them, his only hope of rapport is to reduce the result back to blankness, and I doubt if he can do that; in other words, he and the painter do not share the picture as an object because the painter has not yet seen it. He can, however, judge the work on its merit before him without trying to enter into partnership.

It is possible that the main contribution of this form of painting will be limited to this sharpening of the difference between creator's action and beholder's judgment, which in turn could be extended to our viewing of objective art.

Manchester. OLIVER JELLY.

LEUKÆMIA DEATHS IN COUNTIES

County	1947–49		1950–53		1954–57		% increase in rate 1950–53/ 1954–57	% variation in rate 1947–49/ 1954–57/	Average annual deaths
	Deaths	Rate per 100,000 population	Deaths	Rate per 100,000 population	Deaths	Rate per 100,000 population			
Cambridge	26	3·4	39	3·7	56	5·2	+ 39	+ 53	11
Durham	152	3·5	228	3·7	304	5·1	+ 38	+ 46	62
Cumberland	22	2·5	35	3·1	56	4·9	+ 59	+ 96	10
Westmorland	12	6·0	5	1·8	12	4·5	+140	− 25	3
Brecon	12	7·3	8	3·5	11	4·9	+ 38	− 33	3
Caernarvon	10	2·7	15	3·1	27	5·5	+ 80	+103	5
Montgomery	5	3·6	11	6·1	18	10·0	+ 65	+178	3
Monmouth	36	2·7	53	3·1	87	5·1	+ 65	+ 89	16
England and Wales ..	4644	3·8	7923	4·5	9093	5·1	+ 13	+ 34	1969
Cornwall	44	4·4	71	5·2	69	5·0	− 4	+ 14	16

PROCAINAMIDE AS A MUSCLE RELAXANT

SIR,—This letter describes a trial of procainamide as a skeletal muscle relaxant in a number of neurological conditions characterised by spasticity or rigidity. Results were on the whole disappointing, but since appreciable benefit was given to some patients, they are worth reporting briefly.

The observation which prompted the trial was this. A patient suffering from syringomyelia had an unusual spastic paraparesis. The rigidity of his legs as he stood was so severe as almost to forbid his taking a step, but when he lay in bed the leg muscles felt quite normally flaccid to the hand. With any attempted movement, active or passive, the limb would at once lock rigidly. It was clear that whatever might be the site of the lesion and the effect of posture, hypertonicity was appearing in response to proprioceptive impulses from the muscles—i.e., from the muscle spindles. Arguing that muscle spindles are modified muscle fibres, and that procainamide may lessen the "irritability" of muscle by stabilising the muscle-cell membrane, it was thought that the spasticity might be eased by this drug even though the spindles were not primarily at fault. The response was gratifying. Under treatment with procainamide, the man was able to walk slowly with elbow-crutches, and could climb into bed where before he had had to topple on to it stiffly and roll himself in.

Procainamide was therefore offered to other patients with muscular rigidity, and apparatus was contrived which might measure any improvement objectively. Unfortunately, where benefit was given the lessening of spasticity was never nearly great enough to be measured satisfactorily.

Procainamide was given by mouth, initially 250 mg. four times a day. If benefit followed, a further effect might be had by increasing to 500 mg. four times a day. Higher dosage never gave more relaxation.

Several patients reported untoward effects. 2, both suffering from disseminated sclerosis, said that their spasticity was increased while they were taking the tablets. 2 others discontinued treatment because of feelings of malaise and "uselessness". 8 patients complained of burning epigastric discomfort soon after taking the tablets. One man, who had a moderately severe spastic paraparesis due to disseminated sclerosis, experienced a sudden return of sexual potency which he attributed to the procainamide. No patient reported the unpleasantly vivid dreaming which has been described by Geschwind and Simpson,[1] and none made particular complaint of insomnia. Blood examinations showed no important changes.

Procainamide is bitter, and many patients found the tablets unpleasant to take. Further, the tablets are apt to soften and so become even less palatable if they are not kept in a tightly closed container. These inconveniences might be overcome by a suitable coating.

Results

Spastic hemiparesis following a cerebrovascular accident.—10 patients were given procainamide. 4 felt that there was a little lessening of their stiffness. It is unlikely that there was any real effect.

Spastic paraparesis due to disseminated sclerosis.—44 patients were given procainamide. 18 said at once that they were easier in movement, and on examination it was easy to be convinced that the limbs were indeed rather less spastic. 6 patients denied any benefit, but when the drug was stopped, decided that they *had* been helped and asked that it be continued. 20 patients were sure that they had had no benefit.

Flexor spasm.—16 patients were treated. The spinal cord lesions were of various causes, disseminated sclerosis being the commonest. All had some benefit, and in particular there was relief from pain. Flexor spasm can be exceedingly painful, a constant soreness in the inner thigh and at the origin of the adductor muscles being exacerbated with each flexing movement of the thigh. Procainamide either abolished this pain or reduced it to a level of tolerable discomfort. The incidence of the spasms was probably not affected, but most patients described them as being less severe or less powerful.

Motor-neurone disease.—14 patients were treated. The drug was given to ease the aching muscle pain, and to stop the painful cramps which are particularly distressing in the forearms and in the small muscles of the hands. In this it was very effective: pain was abolished in every case and cramp either did not occur or was slight. The effect was very much greater than had been had from quinidine pushed to the limit of tolerance.

Parkinsonism.—Procainamide was given to 20 patients with parkinsonism from various causes. No benefit whatsoever was obtained.

Procainamide is therefore of considerable use in easing the distress caused by flexor spasm (though it is no substitute for treatment by physical measures). In motor-neurone disease it was effective in stopping muscle pain and cramp.

The relaxant effect in spastic paraparesis is more doubtful. Rigidity of the legs varies greatly in the same patient from time to time: a full bladder, urinary infection, or skin irritation from incontinence may all increase it. Good physiotherapy may lessen it. The worth of any muscle relaxant is exceedingly difficult to assess. Procainamide probably did help a number of patients, and in my opinion its effect was comparable to that of the commonly used proprietary relaxants. Since it is no more expensive than most of these, it is worth bearing in mind. In parkinsonism and in spastic paresis following cerebrovascular disturbance the drug was of no value.

I wish to thank the Medical Committee of the Maida Vale Hospital for permission to publish details of these cases.

Maida Vale Hospital,
London, W.9. J. C. PHEMISTER.

1. Geschwind, N., Simpson, J. A. *Brain*, 1955, **78**, 81.

A CARDIAC DEFIBRILLATOR: A WARNING

SIR,—Attention has already been drawn in this correspondence to the dangers of using mains electricity directly for cardiac defibrillation and it cannot be too highly stressed how dangerous this practice is.

As was pointed out by Dr. Kelly (Oct. 17), the neutral pole of the electricity supply is connected to earth and there is therefore a danger of serious and possibly lethal electric shock due to accidental contact with any conductor connected to the live pole. Such contact could occur, if the mains supply is used for defibrillation, by touching the patient or any metal in contact with him or be due to defective insulation of the electrodes or their connections.

Serious burning may be caused if the timing of the current pulse is at fault and if Dr. Butler's suggestion (Oct. 24) is followed, failure of the control switch on the electrical outlet might have disastrous results. If direct connection is made to the electrical outlet a circuit fuse may be blown by accidental contact between the electrodes with the consequent loss of the supply and, if I may quote Dr. Butler, the connection of the control switch in the neutral instead of the live conductor could "prove remarkably lethal".

The circumstances under which a defibrillator is used would appear to make it most undesirable for the users to have to give special consideration to their own safety and that of their helpers and if a defibrillator is required it should incorporate an adequately insulated, double-wound, mains-isolating transformer to provide an earth free output and a reliable timing device to limit the time of application of the defibrillating current.

Ministry of Health,
London, W.1. P. M. HARMS
Electrical Safety Engineer.

RISKS ASSOCIATED WITH MODIFIED ELECTROPLEXY

SIR,—The letter from Dr. Rahill (Oct. 17) is of special interest as being the first recorded unfavourable opinion of ectonus from anyone who gives the assurance of having applied that technique strictly in the recommended way. To do this means that in all except perhaps a few mild cases, the method is applied intensively for a period averaging 7 to 10 days, usually one dose being given each day. The most essential feature of the orthodox application of this technique, especially in the treatment of schizophrenics, is that it should be pushed to the extent of producing a confusional state in the patient. If Dr. Rahill was using ectonus in this way over a period of 2 years, one would expect him to be able to report a number of successes especially if schizophrenics and manic-depressives were the main part of his selections. If he had used ectonus in planned combination with phenothiazine drugs, I believe his results would have been still better.

Ectonus used intensively and preferably in the form of ectonus-phenothiazine therapy (E.P.T.) can certainly produce recoveries in a short time. Many of these recoveries do not seem to be obtainable by any other methods.

In the treatment of the commoner psychoses any of the well-known methods of electrotherapy—i.e., traditional E.C.T., modified E.C.T., fused dosage ("intensified"), or ectonus—can produce cures when used intensively. In the case of modified E.C.T. this is assumed to be true, since there appears to be no record of anyone using this method intensively. It is clear that the two injections daily and the electrical dose for a period would be a severe physical strain on any patient. On the other hand, Jacoby [1 2] has described the intensive use of ordinary E.C.T. to which he applies the term "regressive shock therapy". In this method not only is the E.C.T. given daily to the point of producing a confusional state, but most of the patients get several daily doses. From his description the method is a rather drastic one and the strain on the patient is severe. He advises the use of this technique mainly in chronic paraphrenics who have failed to respond to other therapies. But striking cures result, he says, and justify the relatively serious physical risks.

The two methods of electrical modification of the convulsion introduced by Dr. R. J. Russell (ectonus and fused dosage) have the very great advantage of being well tolerated by a great many patients of almost all ages when given intensively. This is the factor which makes these methods, especially ectonus, capable of wide use in the cure of psychoses.

Electrotherapy is a valuable means of relieving symptoms. But for the psychoses it is a curative agent only when given intensively.

Lennox Castle Hospital,
Lennoxtown, near Glasgow. ALLAN A. MACDOUGALL.

SIR,—I wish to draw attention to three articles published during the past year, in which most of the questions posed by recent correspondents have been answered.

(1) The first [3] was concerned with the results of a questionnaire circulated to 55 hospitals in 1957 to ascertain which techniques of giving E.C.T. were used throughout this country. It followed the action, Bolam *v.* Friern Hospital Management Committee, in which a number of medical witnesses failed to agree upon a uniform E.C.T. technique, and contained a review of the literature showing a similar disagreement amongst previous authorities.

The results showed that muscle relaxants were used at 85% of the hospitals contacted. At 60% E.C.T. was modified with thiopentone and succinylcholine ('Scoline'), and at 15% with thiopentone and suxethonium ('Brevidil E'). At only 8% was E.C.T. modified with suxethonium alone, and the ectonus technique without relaxants was used at 6% of hospitals. These findings were considered to be of value should any further cases of litigation arise. It is emphasised that these figures refer to male patients only.

The questionnaire also revealed that anæsthetists were in attendance at only about 50% of the mental hospitals when E.C.T. was modified with anæsthetics and relaxants, but at most teaching hospitals the presence of an anæsthetist during the performance of electroplexy was obligatory.

The results indicated the necessity for ascertaining data about the best techniques of giving E.C.T., and a research scheme comparing different methods has been in operation at Banstead Hospital, and will be reported in due course.

(2) The second [4] was concerned with the results of another questionnaire sent to the same hospitals. The causes of death of 9 patients who had died following E.C.T. during 1956 and 1957 were analysed, and indicated that the predominant mode of death was cardiovascular. These 9 deaths were distributed over more than a quarter of a million treatments. The conclusions were that the fatality-rate from E.C.T. was extremely low (1 death in 28,000 treatments), and that modification of the convulsion did not affect the risk to life.

(3) In the third paper,[5] 3 patients who suffered from prolonged apnœa after suxethonium-modified E.C.T. were reported for the first time, although several examples following the use of suxamethonium had been previously described. All these patients received E.C.T. without a general anæsthetic, and there were no respiratory complications when it was given unmodified. Serum-pseudocholinesterase estimations gave low levels in all the patients, and 1 of them did not breathe spontaneously for an hour following treatment.

The causes of this condition were discussed in detail, and some points about prevention and treatment were given. It was suggested that P.A.M. (pyridine-2-aldoxine methiodide), which successfully reverses some of the symptoms of alkyl-phosphate ('Parathion') poisoning instantaneously, and restores the serum-pseudocholinesterase to normal levels, might act as a specific antidote in these instances of prolonged apnœa, but it has not so far been possible to obtain this preparation in a purified form for intravenous use.

I hope these articles will be of general interest.

Banstead Hospital,
Sutton, Surrey. J. C BARKER.

SURGERY FOR CHRONIC MYOCARDIAL ISCHÆMIA

SIR,—The article by Dr. Kauntz and his colleagues (Oct. 24) draws welcome attention to the relief which surgery can give to chronic myocardial ischæmia.

Acceptance of surgical treatment for angina pectoris has been slow for several good reasons. Hopes of devising an operation to bring blood to the heart from outside sources have so far proved vain. The large variety of techniques advocated tends to produce scepticism. The disease runs a variable course and objective evaluation is difficult.

Nevertheless Beck has demonstrated the value of intercoronary anastomoses and shown that they can be promoted by operation. He has achieved good results with low mortality in a large number of patients.[6] One of us has had the opportunity of working with Beck and has seen many of these patients. Convinced of the value of this operation in selected patients we began to apply it in 1957.

1. Jacoby, M. G. *Brit. med. J.* 1958, i, 282.
2. Jacoby, M. G., Babikian, H. M. *N.Y. St. J. Med.* 1958, **58**, 2965.
3. Barker, J. C. *J. ment. Sci.* 1958, **104**, 1069.
4. Barker, J. C., Baker, A. A. *ibid.* 1959, **105**, 339.
5. Barker, J. C., May, A. *ibid.* p. 496.
6. Beck, C. S., Leighninger, D. S., Brofman, B. L., Bond, J. F. *J. Amer. med. Ass.* 1958, **168**, 2110.

Three of the four patients on whom the Beck operation was performed in 1957 have had an excellent result and are still virtually free of symptoms. But subsequent mortality in bad-risk patients has influenced us to try Thompson's procedure [7] which avoids a major thoracotomy. Early results have been encouraging and may prove to be comparable to those obtainable with the Beck operation.

Southmead Hospital
Westbury-on-Trym, Bristol.

GORDON MATHER
MICHAEL WILSON.

CLASSICAL HÆMOPHILIA OR CAPILLARY DISORDER ASSOCIATED WITH ANTIHÆMOPHILIC GLOBULIN DEFICIENCY?

SIR,—Dr. Valberg (Sept. 26) asserts that there seems to be sufficient evidence to consider the family described by Treves,[8] Handley and Nussbrecher,[9] and myself [10] as an example of a capillary disorder associated with antihæmophilic globulin (A.H.G.) deficiency and not classical hæmophilia. He cites in evidence the presence of a positive tourniquet test in 3 patients, a prolonged bleeding-time in 1 subject, and anomalous inheritance in the first four generations. In my opinion his conclusions are probably incorrect and are certainly premature.

The positive tourniquet tests were recorded as 120 petechiæ in one case, 20–30 in the second, and 15 in the third. Since 10 petechiæ were regarded as being compatible with normal this was really only one test which was strongly positive. Positive results with this test are not infrequent in even apparently normal subjects and are not rare in some common pathological states, such as hypertension and diabetes.[11] Their importance need not be overrated. The prolonged bleeding in 1 case can also be viewed in a similar light. It is true that it is an infrequent finding in classical hæmophilia but the test is not easy to standardise. "False" positive results due probably to technical causes can and do occur in hæmophilia. In one series prolonged bleeding-times were encountered in almost half of the 19 A.H.G.-deficient subjects, and in only 1 of these did the diagnosis of a combined vascular and humoral defect seem justified.[12]

In most cases it is easy to distinguish those patients with A.H.G. deficiency who have a combined vascular defect from those with classical hæmophilia. The bleeding diathesis is usually not nearly as severe in the former group, and hæmarthroses are relatively much less frequent. Valberg and Brown [13] found no case with hæmarthrosis in 15 patients, while in a recent review of 20 patients there were only two with joint bleeding.[7] The highest incidence of hæmarthrosis I have been able to find has been 3 out of 9 patients.[15] Residual permanent joint deformities have only rarely occurred. In contrast to this Treves' family had a severe bleeding diathesis, many of the affected males had had hæmarthrosis with residual joint deformities, at least 4 of the 5 affected females had repeated attacks of joint swelling, and residual deformities with X-ray changes were recorded in one of these.

The severity of the clinical picture and the presence or absence of hæmarthrosis is probably largely dependent on the level of circulating A.H.G. Most of the cases of capillary disorder with A.H.G. deficiency who have had levels of circulating A.H.G. recorded have not had less than 1–2% and many have had considerably more. But it is conceivable that patients will be described who have a capillary disorder and no demonstrable circulating A.H.G. I have seen 1 such patient in a series of over 100 hæmophilics. He was a man with a story of bleeding from childhood, who bled moderately severely from cuts, who had had hæmarthrosis and who 20 years ago had nearly died from hæmorrhage after surgery for obstructed inguinal hernia. Recently he required large quantities of fresh plasma and bovine A.H.G. for abdominal section for the removal of a colonic polyp. He had a brother who had died from hæmorrhage at the age of 6 years. He has had a long bleeding-time and a positive tourniquet test recorded on numerous occasions. His A.H.G. level is zero.[16]

I feel that the final diagnosis in Treves' family will depend on genetic considerations. There is no doubt that the anomalous inheritance in the first 4 generations is not compatible with hæmophilia as we know it today. I merely repeat that these patients died many years ago and the history of bleeding especially in the 1st, 2nd, and 4th generation was very scanty and amounted to little more than a tradition in the family that they were bleeders. The inheritance after the first four generations could be that of an autosomal dominant but it is not incompatible with sex-linked inheritance as postulated. Further study of later generations should soon put this matter beyond dispute one way or the other. If it is dominant inheritance then affected females will again be encountered. In the absence of another mating between a potential carrier of bleeding disease and an affected male, such females will support Dr. Valberg's contention. If the severe bleeding state is confined to males while females show no more than might be anticipated from heterozygotes in a hæmophilic family then the diagnosis of hæmophilia will receive powerful support. I think it is still correct to say that a familial bleeding disorder inherited as a sex-linked recessive characteristic, is, on present knowledge, either hæmophilia or Christmas disease.

The subject in dispute will be resolved with time and increasing knowledge. On the available evidence I feel that Dr. Valberg is probably incorrect. At the very least the matter should be left sub judice.

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University of Cape Town,
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Cape Town.

C. MERSKEY.

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9. Handley, R. S., Nussbrecher, A. M. *Quart. J. Med.* 1935, **4**, 165.
10. Merskey, C. *ibid.* 1951, **20**, 299.
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12. Harmon, M. C., Zipursky, A., Lahey, M. E. *J. Dis. Child.* 1957, **93**, 375.
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15. Nilsson, I. M., Blombäck, M., Von Francken .I. *Acta med. scand.* 1957, **159**, 35.
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Appointments

BAMFORD, F. N., M.B. Manc., D.C.H., D.P.H.: senior M.O. (care and aftercare services), Bradford.
BURNE, B. H., M.R.C.S., D.P.H.: senior assistant M.O., Buckinghamshire.
CHOWDHURY, A. K., F.R.C.S.: senior casualty officer, Royal Infirmary, Doncaster.
CLARKE, JOHN, M.B. Manc., D.P.M.: senior assistant psychiatrist, Saxondale Hospital, Radcliffe on Trent, Nottinghamshire.
CLIFFE, PERCY, M.B., PH.D. Lond., B.SC. Wales: consultant in charge, department of clinical measurement, Westminster Hospital, London.
COOK, H. P., M.B. Lond., M.D.S., F.D.S. R.C.S.: assistant dental surgeon, Middlesex Hospital, London.
HINDE, JEAN M., B.M. Oxon., D.OBST.: assistant M.O./school M.O., Devon (Tiverton/Crediton area).
KEITH, DONALD, M.B. Edin., M.R.C.O.G.: consultant in obstetrics and gynæcology, Pontefract, Wakefield, and Goole area hospitals.
LEE, G. DE J., M.D. Lond., M.R.C.P.: consultant physician, United Oxford Hospitals.
MCKENNY, J. G., M.B. Belf., D.OBST., D.P.H., D.T.M. & H.: senior assistant M.O.H. and school M.O., Gloucestershire.
MURTAGH, G. P., M.B. Belf., F.F.A. R.C.S., D.A.: part-time consultant in anæsthetics, Hull A and B hospital groups.
PALLISTER, W. K., M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Middlesex Hospital, London.
ROBB, H. P., M.B. Aberd.: assistant psychiatrist (S.H.M.O.), Aycliffe Mental Deficiency Hospital, Heighington, Darlington.
WOLLNER, LEOPOLD, M.B. Lond., M.R.C.P.: consultant physician in geriatrics, Aylesbury/Amersham/High Wycombe area hospitals.

Surrey County Council:

GAY, P. N., M.B. Lond., D.O.: part-time ophthalmic surgeon.
MACFARLANE, L. HELEN, M.D. Lond., D.P.H., D.O.M.S.: part-time ophthalmic surgeon.
ROMANES, G. J., M.R.C.S., D.O.M.S.: part-time ophthalmic surgeon.

Parliament

Parliamentary Programme

THE first session of the new Parliament was opened on Oct. 27 by a Royal Commission. The Queen's Speech, which was read by the Lord Chancellor, outlined the legislation which the Government plans to introduce. These will include measures to modernise the law in Scotland relating to mental health and to provide for the registration of certain professions auxiliary to medicine. It is expected that these professions will be: chiropodists, dietitians, medical laboratory technicians, occupational therapists, physiotherapists, radiographers, remedial gymnasts, and speech therapists.

It is also hoped to make further advances in penal reform, and a Bill is to be introduced to provide more effective means of dealing with young offenders and to extend compulsory aftercare to prisoners who, by supervision on discharge, may be prevented from reverting to crime. Further relaxation is also promised in the earning rules for pensioners and widowed mothers.

The Speech from the Throne also mentioned that a Cabinet Minister had been specially entrusted with responsibility for development in research and other scientific activity "in recognition of the place of science and technology in the modern world". Lord Hailsham, the new Lord Privy Seal, has been charged with this duty, which will include ministerial responsibility for the Medical Research Council. As Lord Hailsham sits in the Upper House, Mr. Derek Walker-Smith, who remains at the Ministry of Health, will still answer for the M.R.C. in the Commons. Miss Edith Pitt, formerly joint parliamentary secretary to the Ministry of Pensions and National Insurance, has succeeded Mr. R. H. M. Thompson as parliamentary secretary to the Ministry of Health.

Youth Near the Helm

On Oct. 30 the main theme of the debate on the Queen's Speech was the needs of youth, especially their leisure. Mr. ANTHONY GREENWOOD, who opened the discussion, was anxious that the problem of delinquency should be kept in perspective, for though the number of offenders was far too high it was infinitesimal compared with the total of 4 million teenagers we had in this country. Most of our young people were hard-working and sober. They were better educated and more prosperous than their predecessors. They matured physically much earlier and had a refreshing poise and self-confidence. But in three to five years there would be another million teenagers who would need jobs. Already training facilities were a bottleneck. Were the Government encouraging apprenticeship training? What were they doing about the recommendations of the Gowers report about the working conditions of young people. Of every 100 young people about 20 remain at school after the statutory leaving-age. For them there were reasonable facilities for sport and leisure. For the other 80 facilities were lamentably inadequate. What standard of facilities did the Minister of Education believe that the youth services should provide and what help would he give them?

Dr. DONALD JOHNSON thought that we must recognise that we had a generation of young people growing up which probably had no tradition behind it in the use of leisure. They were recipients of benefits which had come, by and large, through outside agencies, such as the Welfare State, and for which they had not been called to shoulder any responsibilities of their own. They had a feeling about those benefits that they had not any voice in the way in which they were conferred.

The most baffling problem was that there was a large section of our youth which could not be reached. It was withdrawn, unapproachable, and even resentful of efforts to help it. The clever and more brilliant among our young people were creamed off and given opportunities, but they were not the ones who constitute the problem. It was those who were left behind with a smattering of education and then brought forward into a society to which many of them felt they did not belong. The problem of not belonging was a psychological one. We had a considerable mass of young people who suffered from boredom, and in many this boredom alternated with curious outbreaks of violence. Whether we were trying to provide work, interest, or leadership, we should make no headway unless we adjusted our society to make it a more attractive proposition for young people to share in it.

Mr. LEO ABSE said that many reports about juvenile delinquency tacitly assumed that it was bewildering that at a time when there was more general material prosperity there was also more delinquency. He was convinced that there was a myth in existence that led people to believe that the benefits of prosperity were reaching everybody. In fact if you examined delinquency in a large city, it became clear that it was related to inadequate homes in slum areas. The main basis of juvenile delinquency was our problem families whose children were living within a grim form of subculture. We needed social workers urgently and he hoped that we should speedily hear something about the establishment of the national council for social work which the Younghusband Committee had proposed.

Sir DAVID ECCLES, the Minister of Education, suggested that our teenagers had the most difficult task of any group in the community in adjusting themselves to the material security and the material gains of an expanding economy. If a comparison was made between the spending power of different sections of the community, between pre-war and the present day, it was the teenagers who had gained far the most in relative terms. It was all the more satisfactory to find that the very great majority of the young today were using their new opportunities and were enjoying their work and their leisure. But though there was so much to be proud of, there was also quite a bit to be disturbed about. Some boys and girls did not find it easy to adjust themselves as soon as school was over to the new age of earning £5 a week, or something like it, and to the new freedom from restraints. He was sure that the way to help these young people was not to treat them as a separate problem. They were not outsiders; they were simply members of a generation all of whom had not yet found the way to use their leisure to their own real satisfaction. What saddened him about them was really their loneliness. They might go rushing about in groups, but if one talked to them one found that they did not seem to have a real friendship with those with whom they spent their evenings. It was sad also to see how defiantly they drifted in and out of jobs and in and out of trouble.

He was sure we could not put all this down to the war. He was sure it would be wrong to believe, as some people said, that we were just passing through a temporary bad patch that would clear itself up in a year or two when all the children who were born in the years of war became 21. He believed the causes lay deeper and elsewhere. He thought the answer was that the teenagers of today had more leisure and more cash than ever before, but at the same time they had more liberty and far less moral guidance on how they should behave towards each other and towards society. At the very moment when these young people needed special care and guidance on how to use the new opportunities, many of their elders had become uncertain of what was good and what was bad in behaviour and in morals. One reason why many of these teenagers seemed so determined not to take any advice, determined not to be organised in any way in their activities, but rather to insist, and often truculently, on going their own way, was that over the past twenty years or so they had seen that their elder brothers and sisters looked for guidance and found too often that grown-up people were either cynical or silent.

Our policy had to be framed for youth as a whole, not for those who happened to be called problem children for the time being. The Government had undertaken to increase the material resources available to the youth service, and they were determined it should be much more than a rescue operation for an awkward or tiresome minority. But the Govern-

ment could not, simply by spending public money, solve that part of the problem which was largely a failure of morals. They expected to receive much help from the Crowther and the Albemarle reports. The Crowther report was in the hands of the printers and should be published at the end of next month at the latest. He hoped that the Albemarle report would be published during the latter part of the Christmas recess. But one or two principles, on which all were agreed, had already emerged. It followed from the independent attitude of the great section of young people who were not now touched by youth organisations that, if we were to bring them in, we should have to look for ways and means by which they did most of the work for themselves. We could not hope to impose on them any kind of national or ready-made system of leisure activities. We should have to work through the voluntary organisations and the local authorities, filling in the gaps and strengthening their resources. We should be prepared to let those who had been working in this field have the resources to experiment in different, and probably novel, directions. He was impressed by the need to smooth the transition from life in the schools to the world of earning and spending, and he thought that we must make a special effort to bring the schools and the youth services together. The education service had always seemed to him a long strung-out line of advance, and perhaps in this Parliament we could give a push on the front of the youth services.

Shortage of Maternity Beds in Manchester

On the adjournment on Oct. 29 Mr. ERIC JOHNSON drew attention to the shortage of beds for confinements in Manchester. In itself it was serious enough, but it had the further ill effect of leading to a diversion of beds in the gynæcological section of St. Mary's Hospital. If a woman wanted to have her first baby in one of the three main Manchester hospitals she had to be seen during the first ten weeks of her pregnancy or it would be too late for her to get in unless the case was quite abnormal. The proportion of institutional confinements in 1957 for Manchester mothers was 59·1%, compared with the national figure of 64·5% and the 70% which the Cranbrook Committee recommended for future planning.

There were at present 345 lying-in beds in Manchester, Mr. Johnson continued, and in 1958 there were 8675 confinements or 25·14 per bed per year. That was far too many, and led to undesirable and dangerous expedients. For example, there was a tendency to use antenatal beds for ordinary lying-in patients. There was a further difficulty of keeping beds for isolation purposes. There was sometimes serious overcrowding. Patients had to remain in the labour room for a very long time after their delivery while they were waiting for a bed from which a lying-in patient had just been discharged. That, in turn, led to the undesirably early discharge of lying-in patients, and to restriction of ward cleaning and decorating programmes. It had been suggested that a more rapid throughput of patients was the solution of Manchester's problem, but they were already being discharged in as little as five days from the regional-board hospitals and three days from the teaching hospitals.

According to his calculations some 136 more maternity beds were needed in Manchester. He understood that the Minister had accepted three years ago the proposal to build a new hospital with 135 maternity beds. That was inadequate. It would not meet even the present deficiency. Even if building the new hospital started right away, there was still an urgent need to do something at once. By far the best way—and he was supported by all medical opinion in the city—was the provision of additional general-practitioner beds. However, more general-practitioner beds was only a stopgap. He agreed that Manchester's urgent and imperative need was for a new maternity hospital. He hoped that when that hospital was built a general-practitioner annexe would be provided.

Miss EDITH PITT, speaking for the first time as parliamentary secretary to the Ministry of Health, said that the Minister was fully aware of the deficiencies, both in quality and quantity, of maternity accommodation in Manchester. As a result of the Cranbrook report he had last July asked hospital authorities, including those of Manchester, to review their maternity accommodation. The final conclusions about the needs of Manchester must await the result of the review, but meanwhile action was being taken. A new maternity unit was being provided at Withington Hospital, and the first phase of a new hospital now being planned for building at Baguley would include another new maternity unit. Taken together, these two projects would increase the number of available maternity beds by about 70. Within the next few days the Minister would invite the board of governors of St. Mary's Hospital to begin the planning of the first phase of a new hospital so that the building might begin as soon as planning was completed. In the main, the new hospital would be a replacement of the old, but it was expected that about 20 additional antenatal beds would become available. These three projects would increase the total of maternity beds of all kinds under the National Health Service from about 370 to 460, or by nearly 25%.

Obituary

JONATHAN CAMPBELL MEAKINS

C.B.E., M.D. McGill, LL.D. Edin., F.R.C.P., F.R.C.P.(C.), F.R.C.P.E., F.A.C.P.

Dr. Meakins, who held chairs of medicine at McGill University and at Edinburgh University, died at the Royal Victoria Hospital in Montreal on Oct. 12 after a short illness. He was 77 years of age.

He was born in Hamilton, Ontario, and graduated in medicine at McGill University in 1904. After two years of internship and residency at the Royal Victoria Hospital he spent a year with Dr. Rufus Cole in the department of bacteriology of Johns Hopkins, and two years in the department of pathology of the Presbyterian Hospital in New York under Eugene Opie. He then returned to McGill and the Royal Victoria Hospital with the orthodox training expected at that time of a physician who had academic ambitions. He quickly showed, however, that his outlook on medicine was far from orthodox. He had an inquiring mind and realised the importance of the physiological approach to medical problems. He was appointed director of the department of experimental medicine in McGill in 1912 but he soon resigned from this appointment and left for England to work with Thomas Lewis and James Mackenzie.

He returned to Montreal in July, 1914, in time to enrol in No. 3 General Hospital which sailed for England in May, 1915. But his real interest was still in experimental medicine and by the end of that year he had joined his old friend Thomas Lewis to study D.A.H. During the next three years Meakins belonged to a team which investigated the physiological problems which arose from gas warfare and other hazards. Other members of the team were Lewis, Sir Henry Dale, Haldane, Barcroft, and Cushny.

By the end of the war in 1918 Meakins was widely known as a sound physician who was also a brilliant investigator and who had the drive, energy, and personality of the born leader, and soon after his return to Montreal in 1919 he was offered the Christian chair of therapeutics and clinical medicine at Edinburgh University. Of his full and varied life there a colleague writes:

"Meakins was one of the first to introduce scientific methods of research into the Edinburgh Infirmary, and the laboratories which he planned are still evidence of his energy and foresight. He also struck a new note in the professoriate. It would not be unusual for him, with his charming wife, to enjoy a jovial evening with the students and next morning to deliver a fascinating lecture on the application of physiological prin-

ciples to disease and then conduct a breezy ward-round, attended in those congested post-war days by 30 or 40 clerks. Yet he found time to write the first book on respiratory function in disease and he was a member of Barcroft's expedition to the Andes which made the first comprehensive study of the effects of high altitudes on man".

In 1924 Meakins returned to Montreal as professor of medicine at McGill University and physician-in-chief at the Royal Victoria Hospital where he made many changes in the old order. He quickly established himself as one of the leaders of medicine in the North American continent.

In 1929 he was elected the first president of the Royal College of Physicians and Surgeons of Canada and five years later president of the American College of Physicians and Surgeons. The next year he was president of the Canadian Medical Association. At the outbreak of the late war he became deputy director of medical services in the Canadian Army with the rank of brigadier. In 1942 he became dean of the faculty of medicine at McGill University. He was editor of the *American Heart Journal* and his book on *The Practice of Medicine* has some six editions. He was appointed C.B.E. in 1945.

R. V. C. writes:

"Dr. Meakins will be remembered by his colleagues for his magnetic and forceful personality and the prominent part he took in Canadian and North American medicine. Opposition he treated as a challenge which he met with zest and vigour. By those he trained he will also be remembered for his friendly leadership, his integrity, and the stimulation of his quick and accurate mind. But long after his friends and colleagues have followed him, he will be remembered as a pioneer in applying scientific methods to medicine. He will take his place in medical history as the first to make an organised effort to investigate the disturbances of function in diseases of the lung, an effort which culminated in the publication in 1925 of his book *Respiratory Function in Disease*.

"His name will also be recorded in the annals of Edinburgh University and McGill University as the man who introduced an atmosphere of scientific inquiry and research into their teaching hospital."

Dr. Meakins is survived by his wife, a daughter, and a son who is a physician at the Royal Victoria Hospital.

OLIVER FRANK THOMAS

F.R.C.P., D.P.H.

Dr. O. F. Thomas, physician-superintendent of Aintree Hospital, Liverpool, died on Oct. 17 at the age of 60.

He qualified from the University of Manchester in 1924, and after holding house-appointments he became a medical Officer at Broadgreen Hospital. In 1932 he moved to Sunderland as tuberculosis officer to the borough, but the post of superintendent at Broadgreen became vacant a few months later and he returned to take up the post. He was elected F.R.C.P. in 1953. He was appointed to Aintree Hospital, formerly Fazakerley Sanatorium, in 1955.

V. C. C. writes:

"After the formation of the National Health Service Frank Thomas's wide knowledge and experience was fully used by the Regional Board in the replanning of the tuberculosis service in the region and latterly in the organisation of an efficient chest service. He also played his part at national level in this re-organisation through his membership of the Joint Tuberculosis Council and other bodies. O. F. had been in failing health for many months, but he always refused to give in and carried on his work till only a few days before his death.

He will be greatly missed, not only as a consultant, but on the many committees on which he served and where his opinion was much sought after and esteemed".

Dr. Thomas leaves a widow and two daughters.

LUCIEN BRULL

M.D. Liège

Dr. Lucien Brull, professor of clinical medicine in the University of Liège, who died on Sept. 9, has had many friends in this country, ever since he came to University College London as a lauréat du Concours des Bourses de Voyages. He often spoke of the debt he owed Starling in shaping his outlook and future career, and it was this experience in England, and the year which he spent in Strasbourg under Professor Nicloux and Professor Terroine, which convinced him that advances in medicine depend upon the application of physiological methods to its problems, and that the university role of the clinician is one which cannot but absorb his whole time and energy.

Brull became the first full-time university clinician in Belgium; and in 1937 the University of Liège built, to his design and in structural connection with his wards, the research institute which was the tangible expression of his outlook and aims. He made its staffing, equipment, and maintenance self-supporting through a fund dispensed by the university and secured by fees from private patients and contributions from social insurance agencies. Here were accommodated his staff of full-time physicians and medical scientists, many visitors from abroad, and some 30 technicians.

Although his institute was divided into departments each under the direction of a senior member of his staff, the institute, his wards, and his clinics formed an autonomous whole. Every morning at eight o'clock he presided at the brief conference with his staff. He realised the dangers of specialised research divorced from the tempering and nourishing experience of general medicine; and he insisted that all his medical staff, senior and junior alike, should take their full share of responsibility in the wards and outpatient clinics.

Despite the exacting teaching and administrative duties of his office Lucien Brull continued throughout his career to work himself on problems in his special interests; of his part in the advancement of medical science, E.B.V. writes:

"He was the first to demonstrate experimentally the temporary cure of uræmia by kidney grafts, and to elaborate a mechanical heart operating without anticoagulants. Many of the difficulties of cardiovascular surgery derive from the inescapable contact of blood with foreign surfaces, and the principle of Lucien Brull's fundamental work in the field of viviperfusion may later find fruitful application to human needs. He was one of the first to use radioactive isotopes in biological research and therapeutics, and to introduce radioactive iodine in the treatment of thyrotoxicosis. His goitre clinic quickly became one of the world's most active centres for the assessment and treatment of thyroid disease. With the collaboration of Professor Moureau he set up the first blood-bank in Belgium. He founded the International Association of Gerontology and presided at its first congress in Liège.

"The responsibility of his family estate in Campine had given him an intimate knowledge of forestry and agriculture, and at the request of the Belgium Government, and as director of the Mission Interdisciplinaire de l'Université de Liège au Katanga, he had made many trips to the Congo to advise the local administration on land clearance and crop cultivation. He urged the creation of experimental native villages, and on his last visit he saw the first of these in full and happy operation in Haut Katanga. He was firmly convinced that in patient education and the supply of technicians with a vocation to serve lay the road to civilising primitive peoples."

Notes and News

1958 IN THE MENTAL HOSPITALS

DURING recent years the number of voluntary admissions to mental hospitals has steadily increased and in 1958 was 85% of all admissions, the highest figure yet recorded.

Though the number of admissions continues to increase (91,558, compared with 88,943 in 1957 and 55,856 in 1950) the number of patients in hospital at any one time is steadily declining, and the Board of Control [1] considers that this suggests that, owing to more effective methods of treatment, hospital accommodation is being used more effectively and the average length of stay in hospital is being reduced.

At the end of 1958 overcrowding still amounted to 12,932 beds, but had fallen during the year by 1470 beds. The number of whole-time nursing staff had risen by about 1000. The Board welcomes these trends "not only because they are desirable in themselves, but also because they should help to ensure the practical success of the major legislative changes" proposed in the new Act.

THE BRITISH DIET, 1957

THE survey of what we ate in 1957 [2] shows that there has been little change in our diet in the last few years. As a country, we have enough food of the right quality for our needs; no large group of people are seriously underfed. But the survey covers only a small fraction of the population. It analyses the records of food consumption of 8931 households over one week, and, though the households are representative of the country as a whole, the survey cannot tell us how large is the minority of households which have not enough food. Though this minority is certainly only a small proportion, it yet might include thousands of homes. However, it is satisfactory that the *average* intake of households dependent on pensions and of families with four or more children is adequate for physiological needs. The daily average intake of 2587 calories per head is significantly higher than the figure for 1952. Indeed, especially in households with no children the calorie value of the diets seems to be increasingly rising above estimated physiological needs. Unless the level of physical activity has risen or there is more wastage of edible food, it would seem that over-nutrition is increasing.

For the first time the data have been analysed by occupational groups based on the Registrar General's classification. This permits comparison with mortality data. There is, however, little difference between the dietary patterns of the classes. For all households the percentage of the energy in the diets derived from protein, fat, and carbohydrate is 11·6, 38·1, and 50·3 respectively, for professional people 12·2, 39·8, and 48·0, and for unskilled workers 11·5, 36·9, and 51·6. These are the extreme variations. A high fat intake is common to all classes; the professional classes take 20% more fat in the form of butter than the unskilled. Epidemiologists will no doubt want to scrutinise these data carefully for suggestive correlations between the diet and the incidence of degenerative diseases, especially ischæmic heart-disease. But it is doubtful whether they will find much of value, for the general uniformity of the British diet today is the main impression derived from reading the report.

EPILEPSIA

EPILEPSY is a numerically important disorder, disabling patients for many of the activities of modern life. Furthermore road-accident figures assure us that as a post-traumatic condition its prevalence will increase. Accordingly, a journal devoted to the study of epilepsy is welcome. *Epilepsia*, [3] the Journal of the International League against Epilepsy, has been published since 1948; but a new (fourth) series has just been started. With Sir Francis Walshe as its editor-in-chief we may confidently expect a high standard. The first issue contains papers from England, France, Germany, the U.S.A., and Northern Ireland; and the subject matter is equally wide: clinical, physiological, electrical, biochemical, and genetic aspects are all represented.

1. Annual report of the Board of Control for 1958. H.M. Stationery Office. 1959. Pp. 9. 9*d*.
2. Domestic Food Consumption and Expenditure: 1957. Annual report of the National Food Survey Committee. H.M. Stationery Office. 1959. Pp. 137. 8*s*. 6*d*.
3. *Epilepsia:* Journal of the International League against Epilepsy. Fourth Series. Amsterdam: Elsevier Publishing Company. Vol. I, no. 1. March, 1959.

University of London

Mr. W. J. Dempster, lecturer in experimental surgery at the Postgraduate Medical School of London, has been appointed to the readership in experimental surgery at the school. The title of reader in biochemistry has been conferred on Dr. S. P. Datta in respect of his post at University College.

Royal College of Physicians of London

At a comitia on Oct. 29, with Sir Robert Platt, the president, in the chair, Mr. Isaac Wolfson was elected an honorary fellow. It was announced that the college had accepted a gift of £3000 from Dr. F. Parkes Weber to form a trust to be used to promote advances in dermatology.

Dr. Denis J. Williams, Dr. G. B. Mitchell-Heggs, Dr. C. M. Fletcher, and Dr. D. V. Hubble were elected councillors. Dr. J. Forest Smith was re-elected representative on the committee of management. Dr. H. G. Miller was appointed Milroy lecturer for 1961. His subject will be accident neurosis.

The following were admitted to the membership:

A. W. Asscher, M.B. Lond., J. J. Bradley, M.B. Lond., R. B. Cole, M.B. Cantab., J. D. Craven, B.M. Oxon., Michael Dulake, M.B. Cantab., Frank Ellis, M.D. Sheff., Y. E. Hsia, B.M. Oxon., D. T. D. Hughes, B.M. Oxon., J. M. Kendall, M.B. Durh., P. P. Kendall, M.B. Sydney, H. T. R. Koch, M.B. Lond., J. G. G. Ledingham, B.M. Oxon., F. I. Lee, M.B. Lond., A. C. McDougall, M.D. Edin., J. M. Parkin, M.B. Durh., R. W. Portal, M.B. Lond., E. A. Underwood, M.D. Glasg., J. B. Walker, M.D. Western Univ., Ontario.

Licences to practise were conferred on the following, who have passed the final examination of the Conjoint Board:

Gabriel Olugbemiga Alabi, R. M. J. Andrews, C. L. C. Arnold, N. A. Atalla, David Atkins, Howard Baderman, R. B. Barrett, J. G. Bass, J. F. Bedell, Ved Bhushan Bhardwaj, John Brittain, Shelagh M. Broadway, D. M. Broughton, Danai Bunnag, P. E. Burke, A. B. Byles, J. M. Campbell, Rosemary J. Chambers, Marion R. Chaplin, A. F. S. Childs, C. E. P. Clarke, A. B. Clymo, J. C. Collings, G. I. Collins, L. P. Connolly, I. B. Copley, Patricia L. Crawford, Sidney Crown, J. S. Cumming, R. A. C. Davies, Derek Denis-Smith, Kwashivi Agbemabiese Doe, J. M. A. Dyer, F. W. L.-T. Engmann, Diana A. M. Ernaelsteen, P. F. C. Eyre, G. C. Fox, James Fraser, R. W. Gabriel, M. J. Gallant, F. R. Gamman, N. F. C. Gane, J. R. Garrett, David Godwin, R. P. Golding, John Gough, W. A. Gould, W. E. Greaves, Kathleen Green, R. F. Gunstone, Lydia M. Hayes, Brian Higgs, Ann J. Hill, Kenneth Hollinrake, M. J. H. Homewood, D. F. Hopkins, F. T. Horan, M. J. K. Hudson, M. F. Hyatt, E. Oluchukwu Iwenofu, F. H. A. Jago, S. Mahaindra Nauth Jaikaran, Kumari Jai, R. W. John, Josephine I. Johnston, Gillian A. Jonas, E. V. Jones, I. W. Jones, Marion E. Knighton, Eva M. Kohner, David Lamb, D. N. Landon, J. W. Latham, P. W. Lord, J. J. MacMahon, Helen M. McG. McNie, K. S. A. Madgwick, D. M. Marsh, R. D. Marshall, Ann S. Mason, J. S. Mather, L. W. Morrish, D. N. E. Myers, M. J. Noronha, J. Olatunde Oluwasanmi, R. B. F. Orr, W. J. C. Parker, Chandrakant Becharbhai Patel, J. C. D. Plant, G. M. Preston, Max Rendall, D. A. Richards, E. H. Richards, J. R. L. Roberts, J. S. Robinson, I. C. Roddick, Ann T. Roden, Ann Simpson, J. McL. Singleton, Jane Skinner, E. K. M. Smith, M. E. Smith, I. T. Stuttaford, E. J. L. Taylor, C. H. C. Thomas, A. J. Thompson, P. C. R. Tingley, D. J. Tooby, Catherine R. Townsend, John Townsend, R. R. Traynet, Ann Whitfield, Jennifer A. Whitlock, Sarathchandra Piyasiri Wickremasinghe, D. C. Wilson, M. St. G. Wilson, M. B. Wilson, M. C. Winterton, C. C. Wise, Colin Wynne.

Postgraduate diplomas were conferred on those named in the report of the Royal College of Surgeons in our issue of Oct. 17 (p. 622) and on the following:

D.P.H.—Audrey B. Abrams, Srima Nandani Anandaraja, Zeenat Ansari, L. B. Bartlet, Aileen E. F. Benson, Kainthaje Mahalinga Bhat, D. P. Birkett, Margaret I. Blackhall, Joyce O. M. Board, R. V. Boyd, Marita R. Brown, S. A. Bryans, L. M. Burke, R. P. Carrington, J. V. F. Catto, F. L. W. Collings, G. F. N. Collins, G. F. Counsell, Colleen A. Cox, J. H. Darrell, Shivraj Himatrai Dave, Helen A. Davidson, J. G. Davies, Joy Davies, Margaret S. Davies, I. E. Doney, Patricia A. Doran, Sheila M. Eades, P. C. Elwood, J. J. Enright, D. I. K. Evans, Joyce M. Eyre, Abdel Moneim Mohammed Faris, Valerie Farr, B. N. D. Fernando, P. I. Frank, Gajanan Gajre, H. R. Gamsu, G. S. Graham, Naomal Pathmanatha Shradaseela Gunaratna, J. P. Hawe, Jennifer Hill, Irene Holbrook, Margaret Hollands, Ian Briercliffe Houston, Ann L. Hunter, Elizabeth J. Ives, Jacqueline A. Jackson, A. E. F. Jayesinghe, Kizhakeveetil Idikula John, J. K. Johnson, Manmohan Singh Jolly, Barbara D. Jones, J. H. Keen, G. W. Knox, L. Sumanasinghe Kotagama, Sulochana Kanaiyalal Kothari, Mahadeva Krishnaswamy, Shirley A. Leslie, Sheila R. Lewis, Connie K. L. Lim, Gillian B. McCullagh, J. A. W. McKelvey, F. C. McNelis, Ma Mya Kyi, Elsie D. May, Hari Prashad Mehra, D. H. Melville-Swarries, Margaret A. Mills, Isahak Mohammed, Devendra Mohan, Bata Krishna Mukherji, F. A. Murphy, N. M. Morris, Ali Nozari, Yusuf Husayn Nuwayhid, Brenda B. O'Donnell, Gweneth L. O'Reilly, B. J. O'Sullivan, Jean B. Owens, Robert Prosser, K. T. Rackham, Sarojini Sunder-Rajan, B. A. Rapier, Riyazuddin, Sheila M. Russell, Savita Jethalal Shah, Satyavati Sharma, Michael Silver, Anirudh Prasad Singh, Ratneshwar Prasad Sinha, G. H. Smerdon, Ramniklal Vallabhdas Somaia, Catherine I. Soutter, T. I. Stewart, S. G. Sutton, Ursula Tarpey, Ousa Thanangkul, Charmarac Thavarasook, Norma C. M. Theobalds, William Turner, Himatlal Ranchhoddas Vadanagara, J. A. M. Vasey, J. V. Violet, Elizabeth Wales, Hazel M. Wilson, C. D. S. Wood, H. G. Wotherspoon, G. B. Wyatt, Yu-Leung Yeung.

D.T.M. & H.—F. R. Manuel.

University of Edinburgh

The following appointments have been made:

Dr. M. G. Kerr, Dr. E. M. Chinnan, Dr. D. M. Mackinnon, Dr. Heather S. Fulton, and Dr. G. J. Meikle, demonstrators, and Dr. Kazimierz Kuczynski, senior lecturer, department of anatomy; Mr. T. J. McNair, lecturer, department of clinical surgery; Dr. Constance Gibbs, lecturer, general-practice teaching unit; Dr. S. H. Taylor, lecturer, Dr. P. C. Robertson, assistant, department of medicine; Mr. J. H. S. Scott, senior lecturer, department of orthopædic surgery; Dr. A. A. Shivas, senior lecturer, department of pathology; and Mr. Bernard Nolan, lecturer, department of surgical science.

University of Dublin

On Tuesday, Nov. 24, at 4.30 P.M., at the School of Physic, Trinity College, Dublin, Prof. W. Melville Arnott will give the Frederick Price lecture. He will speak on respiratory failure.

On Oct. 29 at Trinity College the following degrees and licences were conferred:

M.B., B.Ch., B.A.O.—James Sainsbury.
L.M., L.Ch., L.A.O.—Lola M. Hamilton.

Royal Australasian College of Physicians

At a meeting in Canberra on Oct. 16, Prof. F. J. Fenner (Canberra) was elected and admitted to fellowship under the special provisions of article 44. The following were admitted to membership:

V. J. Barron, F. M. Elliott, Patrick Harvey, J. R. Johnson, D. W. O'Gorman Hughes (New South Wales); J. M. Court, E. A. Dodge, Joan M. Handley, W. C. Heath, H. Hillman, Ian Maddocks, David McCredie, E. N. O'Brien, G. I. Vidor (Victoria); S. A. Birdseye, G. M. Kneebone (South Australia); J. B. Cope, D. J. Hodges, L. W. L. Jackson, Miles Murphy (Queensland); P. E. Hurst (Western Australia); R. B. Langley (New Zealand); H. O. Wong (Singapore). J. D. Reid (New Zealand) and P. L. Bazeley (Victoria) were admitted under the provisions of article 37.

Faculty of Radiologists

On Friday, Nov. 20, at 4.30 P.M., Sir Charles Dodds will give a Crookshank lecture. His subject will be reflections on cancer research. The Faculty is holding a postgraduate course on Nov. 21 and 22. All the meetings will be at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2. Further particulars may be had from the secretary of the Faculty, 47, Lincoln's Inn Fields, W.C.2.

Hunterian Society

On Jan. 18, at 8.30 P.M., at the Mansion House, London, E.C.4, Prof. C. Walton Lillehei (Minnesota) will give the society's annual lecture. He will speak on recent progress in open heart surgery.

Association of Surgeons of Great Britain and Ireland

The annual meeting of this Association will be held next year in Birmingham on April 7 to 9. The programme will include discussions on open heart surgery and ulcerative colitis.

British Society for Immunology

This society will hold a symposium on Friday and Saturday, Nov. 27 and 28, at 183, Euston Road, London, N.W.1, on persistence of immunity.

International Society for Tropical Dermatology

This society was formed during the International Congress for Tropical Medicine and Malaria. The members of the organising committee are Prof. Aldo Castellani, Dr. G. C. Andrews, Dr. A. C. Cipollaro, and Dr. Frederick Reiss. Further particulars may be had from Dr. Reiss, 870, Fifth Avenue, New York, 21, U.S.A.

British Geriatrics Society

At a meeting on Sept. 24 the title of the Medical Society for the Care of the Elderly was changed to "British Geriatrics Society." It was also agreed to retain the former name as a subtitle. Lord Amulree was re-elected president, Dr. A. N. Exton-Smith hon. secretary, Dr. P. Arnold hon. deputy secretary, and Dr. J. N. Agate hon. treasurer. Dr. T. N. Rudd was elected to the new office of honorary editorial secretary. The next meeting is to be held in Bristol on April 1 and 2. Further information may be had from Dr. Exton-Smith, Whittington Hospital (Highgate Wing), Dartmouth Park Hill, London, N.19.

British Medical Association

On Oct. 28 the Duke of Edinburgh was installed as president of the Association. At a council dinner held that evening at the Guildhall he proposed The Common Health. This choice of toast, he said, suited him because it described a no-man's land between positive good health and active bad health which he regarded as the province of what might almost be a new discipline—the pathology of social diseases. Calling for a combined approach to the problems of communities, he declared that we were trying to apply cures without knowing the causes. Lord Kilmuir, responding, acclaimed the achievements of medicine in the present century. Dr. S. Wand, chairman of council, proposed The Retiring Officers—Dr. A. H. Hall and Mr. Weldon Watts, past-presidents; Sir Arthur Thomson, immediate past-president and now deputy president; and Dr. Ian Grant, formerly chairman of the Representative Body. Dr. Wand announced that the Centre Room at B.M.A. House, where the Duke of Edinburgh had been entertained that afternoon, was henceforth to be known as the Prince's Room. Sir Arthur, in response, spoke of the difficulties of the retired, who must shape their lives so as to be neither nonentities nor a nuisance. Looking forward to an active deputy presidency, he remarked: "You have prolonged my life". Responding to Dr. A. Beauchamp's toast to The Guests, the Archbishop of Canterbury welcomed the renewed activity in the indissoluble partnership between clergy and doctors; and Dr. E. Kirk Lyon, deputy to the president of the Canadian Medical Association, denied that he was a guest at all: he was a member of the family.

The proceedings of the day are reported fully in the *British Medical Journal* of Oct. 31.

Rockefeller Foundation Grants

During the third quarter of 1959 the Foundation distributed $1,556,000. Grants for medical and natural sciences amounted to $546,000 and included a further appropriation of £5,000 to the Medical Research Council towards research on the X-ray crystallography of the proteins, hæmoglobin and myoglobin, at the University of Cambridge, and a grant of £10,500 to Dr. H. Harris and his colleagues at the London Hospital Medical College for their investigations into genetically controlled abnormalities associated with chemical variation in blood-groups.

Calouste Gulbenkian Foundation of Lisbon

During the past six months this Foundation has made, or promised, grants in the British Commonwealth of about £100,000. They include a grant of £4000 to Speech Research for the Deaf, Ltd., to develop a prototype electronic instrument, invented by Mr. G. R. G. Plant, for voice-training of profoundly deaf children (see *Lancet*, 1958, i, 1104). Speech Research for the Deaf, Ltd., is a non-profit association to which Mr. Plant has assigned the patent-rights in his invention.

Mental Health Today and Tomorrow

Speaking at the Royal College of Nursing's conference on this subject on Oct. 28, Mr. Derek Walker-Smith, the Minister of Health, said that in the past the comprehensive term "mental deficiency" had led to the grouping together of patients with divergent needs. In particular, subnormal patients whose intelligence was not greatly impaired, but who were emotionally and temperamentally unstable, had almost always been treated alongside the severely subnormal rather than with neurotic patients whose problems were often more similar to theirs. Changes in the pattern of our psychiatric hospitals would take time; but he hoped to see the gradual development of smaller units and the appropriate re-grouping of patients.

International Congress on Medical Photography and Cinematography

The first international congress on medical photography and cinematography will be held from Sept. 27 to 30, 1960, in Cologne. Further particulars may be had from the Deutsche Gesellschaft für Photographie, Neumarkt 49, Cologne, Germany.

Fellowship for Freedom in Medicine

The annual general meeting of the Fellowship will be held on Saturday, Nov. 14, at 2 P.M., in Caxton Hall, London, S.W.1. Further particulars may be had from the hon. secretary, Dr. E. C. Warner, 45, Nottingham Place, W.1.

Psychosomatic Medicine and Childbirth

There will be an international congress on this subject in Paris in July, 1961. Further particulars may be had from Prof. Norman Morris, Charing Cross Hospital Medical School, London, W.C.2.

Water and Electrolyte Metabolism

A symposium on this subject will be held in Amsterdam on Jan. 8 and 9. Dr. C. P. Stewart will be in the chair, and the British speakers will include Prof. R. A. McCance, Dr. Anne Lambie, and Dr. J. T. Robson. Programmes and application forms may be had from the secretary of the organising committee, Dr. G. Smits, Amstelkade 154II, Amsterdam, The Netherlands.

International Academy of Pathology

An overseas meeting of this Academy will be held next year at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, from June 20 to 24. The programme will include a slide seminar on proliferative lesions of breast and symposiums on the pathophysiology and pathology of the kidney, thyroiditis, and cancer of the thyroid. Further information may be had from Dr. F. K. Mostofi, International Academy of Pathology, Armed Forces Institute of Pathology, Washington 25, D.C., U.S.A., or from Prof. J. Cunningham at the Royal College of Surgeons of England.

London Medical Exhibition

Sir Daniel Davies will open this exhibition on Monday, Nov. 16, at 11.30 A.M. at the Royal Horticultural Society's Hall, Greycoat Street, Westminster, S.W.1. The exhibition will be open from 11 A.M. to 6.30 P.M. (7.30 P.M. on Thursday) till Nov. 20.

University College London

A reception will be held on Friday, Feb. 19, at 6.30 P.M. for undergraduates or postgraduates who entered the college during 1946–50. Applications for tickets should be made before Dec. 31 to the assistant secretary at the college, Gower Street, W.C.1.

St. Thomas's Students' Club

On Oct. 28 Dr. C. F. Harris, vice-chancellor of the University of London, informally opened the extension to this students' club.

The new building, which stands between St. Thomas's House and the site of the new Lambeth Palace Road, cost about £51,000. It has locker and changing-room accommodation for both men and women students, squash-courts, a rifle range, a music room, and facilities for many club activities.

Dr. A. G. Davies has been appointed coroner of Her Majesty's Household in the place of Sir William Bentley Purchase, who has resigned.

The Minister of Health has appointed Mr. L. H. Brandes to be his private secretary. The Parliamentary Secretary has appointed Miss P. A. Hooper to be her private secretary.

Squadron-Leader C. B. Wynn Parry has been appointed Horowitz visiting professor for 1960 at the Bellevue Medical Center, New York University.

Mr. Terence Cawthorne and Dr. Geoffrey Organe are to make a tour of South and Central America and the West Indies, sponsored by the British Council, from Nov. 23 to Dec. 12.

Applications are invited for the Guigoz fellowship and the Nestlé fellowship (1,000,000 fr.) for 1959-60, for research in nutrition. Further particulars may be had from the International Children's Centre, Château de Longchamp, Bois de Boulogne, Paris XVI°.

The British Motor Racing Marshals Club is anxious to add more doctors' names to its medical register. Details may be had from Mr. R. F. Bromley, 6, St. Clare Court, Foxgrove Avenue, Beckenham, Kent.

Diary of the Week

NOV. 8 TO 14

Monday, 9th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Emotions and the Cardiovascular System.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. R. S. McNeill: Gas Diffusion in the Lungs and Abnormalities in the Alveolar Membrane and Capillary Bed.

Tuesday, 10th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Experimental Medicine and Therapeutics.* Dr. J. M. Bishop, Dr. J. F. Nunn: Measurement of Blood Gas Tensions.
8.30 P.M. *Psychiatry.* Prof. Erwin Stengel: A Comparative Study of Current Psychiatric Classifications.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. W. S. Peart: Aspects of Carcinoidosis.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. Richard Doll: Elements of Medical Statistics.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. E. H. Belcher: Control of Radiation Hazards.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. G. C. Wells: Histochemistry of the Skin.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5.30 P.M. Prof. A. Earl Walker (Baltimore): Subcortical Mechanisms in Epilepsy.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Medical School, University of Manchester.) *Surgery.* Mr. R. L. Holt: Modern Trends in the Treatment of Gastric and Duodenal Ulcers.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. K. A. Exley: Pharmacology of the Ascending Reticular Activating System.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Dr. D. M. Green: Immunological Methods and the Detection of Autoantibodies.

Wednesday, 11th

ROYAL SOCIETY OF MEDICINE
8.30 P.M. *Proctology.* Mr. Alan Hunt: Wound Healing and Disruption. (Presidential address.)
POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. W. G. Oakley: Disorders of Carbohydrate Metabolism.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. A. Dudgeon: Virus Diseases.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. H. R. S. Harley: Subphrenic Abscess.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. W. H. H. Merivale: Contribution of Laundering to Hygiene.
OXFORD UNIVERSITY
5 P.M. (Radcliffe Infirmary.) Sir Victor Negus: The Voice of Man. (Litchfield lecture.)
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology.* Prof. W. F. Gaisford: Immunisation Problems in Infancy.
ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow, C.2
9.45 A.M. Opening of three-day conference on the Thyroid Gland.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Mr. W. F. Walker: Surgical Influence on Gastric Physiology.

Thursday, 12th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. A. Dickson Wright: Surgery of the Biliary Passages. (Bradshaw lecture.)
ROYAL SOCIETY OF MEDICINE
5 P.M. *Ophthalmology.* Mr. K. C. Wybar: Eccentric Fixation.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. M. H. F. Wilkins: Molecular Structure of Chromosomes.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. T. Alper, Mr. M. Ebert, Dr. R. H. Thomlinson: Biological Effects of Radiation.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. P. F. Borrie: Erythema Nodosum.
INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
5 P.M. Professor Walker: A Modern View of the Falling Sickness.
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION
2.15 P.M. (1, Wimpole Street, W.1.) Prof. Alfred Meyer: Emergent Patterns of the Pathology of Mental Disease. (Maudsley lecture.)
ALFRED ADLER MEDICAL SOCIETY
8 P.M. (1, Wimpole Street, W.1.) Dr. D. A. S. Blair: The Relationship of Adler's Teachings to Other Schools of Psychiatry.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh, 8.) Dr. Anne Lambie: Syndromes Associated with Potassium Depletion.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Mr. R. J. Brech: Medicine and the Rising Standard of Living.

Friday, 13th

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. G. L. Alexander: Management of Patients with Head Injuries.
4 P.M. Dr. R. S. F. Schilling: Byssinosis in Textile Workers.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Dr. K. G. Rotter: Epistaxis.
5.30 P.M. Prof. F. C. Ormerod: Pathology and Treatment of Deafness.
INSTITUTE OF NEUROLOGY
4.45 P.M. Dr. R. W. Gilliatt: Syncope and the Neurologist.
YORKSHIRE THORACIC SOCIETY
5.30 P.M. (General Infirmary at Leeds.) Dr. J. G. Scadding: Observations on Chronic Interstitial Fibrosis of the Lungs.